QUARTERLY

THE CHICAGO MEDICAL SCHOOL

VOLUME 8 — NUMBER 3

MARCH, 1947

Let your HEAD take you

(The average American today has a choice of just going where "his feet take him", or choosing wisely the course to follow. Let's skip ahead 10 years, and take a look at John Jones—and listen to him . . .)

"SOMETIMES I feel so good it almost scares me.

"This house—I wouldn't swap a shingle off its roof for any other house on earth. This little valley, with the pond down in the hollow at the back, is the spot I like best in all the world.

"And they're mine. I own 'em. Nobody can take 'em away from me.

"I've got a little money coming in, regularly. Not much—but enough. And I tell you, when you can go to bed every night with nothing on your mind except the fun you're going to have tomorrow—that's as near Heaven as man gets on this earth!

"It wasn't always so.

"Back in '46—that was right after the war and sometimes the going wasn't too easy—I needed cash. Taxes were tough, and then Ellen got sick. Like almost everybody else, I was buying Bonds through the Payroll Plan—and I figured on cashing some of them in. But sick as she was, it was Ellen who talked me out of it.

"'Don't do it, John!' she said. '*Please* don't! For the first time in our lives, we're really saving money. It's *wonderful* to know that every single payday we have *more* money put aside! John, if we can only keep up this saving, think what it can mean! Maybe someday you won't have to work. Maybe we can own a home. And oh, how good it would feel to know that we need never worry about money when we're old!'

"Well, even after she got better, I stayed away from the weekly poker game—quit dropping a little cash at the hot spots now and then—gave up some of the things a man feels he has a right to. We didn't have as much fun for a while but we paid our taxes and the doctor and—we didn't touch the Bonds.

"What's more, we kept right on putting our extra cash into U. S. Savings Bonds. And the pay-off is making the world a pretty swell place today!"

The Treasury Department acknowledges with appreciation the publication of this advertisement by

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QUARTERLY

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THE CHICAGO MEDICAL SCHOOL

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Editorials . . .

ANTIVIVISECTION

The fight against knowledge is now being waged throughout the nation by a group of antivivisectionists, who, casting aside all factual evidence are playing on the emotions of a people who do not recognize the value of animal investigation in science. Either unwittingly or with malicious intent, these persons prefer to remain in the caves of darkness. Their time, their money and their effort are all extended in an attempt to break down the firmly established experimental procedures which have become vitally essential in showing investigators that which cannot be used to help man in his war against congenital and acquired pathology. They are the saboteurs of science.

Congressional battles have taken place throughout the country because of an attempt by sympathetic politicians to pass restrictive legislature and thus prevent the continuation of our present studies in drug actions and surgical procedures which might prove useful in the future. Medical men and research men have to rush to state capitals to fight for their lives and waste valuable time which might have been spent in their hospitals and laboratories, telling the story of the medical advancements in the last few centuries and the methods by which they were made.

What are the misconceptions which the antivivisectionists spread to gain a following? We have all heard the sadistic description of the medical student at work. You might think that only those with sadistic traits could enter the field of medicine, when one reads the fantastic details — of screaming animals being butchered by the shiny-toothed, joyous medical student who revels in the victim's pain and death. This is an outright falsehood which could easily be proven incorrect by any visitor to any medical school in the country.

The value of animal experimentation is self-evident to those who have read the history of medicine and to those who keep posted on present day Biological, Physiological, and Pathological investigation. It is up to those who know, to teach the truth to those who are being fed these falsehoods by the anti-vivisectionists.

In order to cope with the present situation it was deemed necessary to organize the National Society for Medical Research under the sponsorship of the Association of American Medical Colleges. The objective of the Society is to advance and encourage research and teaching in Biology, Medicine, Dentistry, Pharmacy and Veterinary Medicine, by informing the public of the necessity and accomplishments of animal experimentation.

This Society has become necessary because of the great and influential activity of the antivivisection society. Antivivisection legislation has had to be defeated in the District of Columbia, Maryland, Pennsylvania, New York, and Illinois.

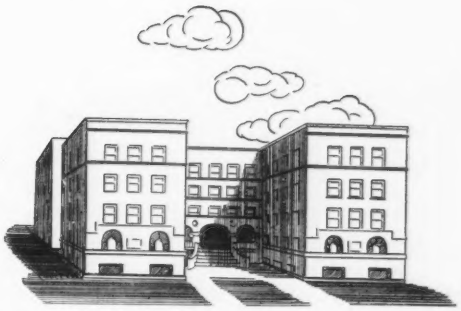
The Staff

The Society proposes to conduct a scientific educational program for a minimum period of five years. It has recently engaged a staff of experienced personnel in the field of public relation and ancillary activities.

The success of the Society requires the moral support of every organization and institution which is directly or indirectly based on animal experimentation.

This has been suggested as:

A Pledge for Antivivisectionists



I am unequivocally opposed to experimentation on animals in medical research. In protest against this practice I pledge myself and my children to refrain from making use of any of the knowledge gained through research in which animals were used:

1) I shall examine with extreme suspicion all medical knowledge.
2) If I or my children become diabetic I shall not use insulin.
3) If I am afflicted with pernicious anemia I shall not use liver extract.
4) I shall never accept a blood transfusion.
5) Vitamins will be as poison to me.
6) I shall use no drugs which have first been tested on animals for strength and purity.
7) If an operation is necesary I shall repudiate anesthesia.
8) These operations shall be anathema to me and mine—
   a. on the heart and its valves
   b. on the lungs
   c. on the blood vessels
   d. on the brain
   e. on the stomach and intestines
   f. on the ovaries and womb
9) If my child is afflicted with rickets I shall look away in pity.
10) I shall not allow my children to be immunized against diphtheria, but shall allow them to strangle with this disease.
11) I shall avoid sulpha drugs and penicillin as I would the plague.
12) I shall make out my will immediately.

Signed .....

REQUEST TO MEDICAL DOCTORS

A wealth of medical knowledge has undoubtedly been uncovered in the fields of former American war activities. New methods of therapy only capable of being devised in times of extreme emergency, have in many cases been found not only suitable but superior to the present day methods of treating entities. Although we are living in a supposedly small world, with the present day communication and transportation facilities as they are, discoveries of great importance frequently lie dormant in the mind of the discoverer or on a piece of paper, awaiting publication, but out of mind's reach of the doctor who might utilize this bit of needed experience or therapy for an individual case he is working on. We can see that even in a world of atomic speed there are many important things which are still crawling along at a snail's pace.

We hope that the Quarterly will be given the opportunity to enlighten its two thousand readers as to some of the strange and successful medical discoveries that our alumni have uncovered on the battle-scarred fields of Europe or in the mud and tropical morasses the armies had to cope with in the South Pacific. Two issues ago we published a letter received from Dr. Murray Paull on some of the unique medicine encountered in three of the concentration camps of Germany. We hope that many more of our alumni follow his example.

BLOOD GROUPS AND THEIR DISTRIBUTION AMONG THE HUMAN RACES*

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THE first observations on the differences between the bloods of normal individuals belonging to the same species were made by Landsteiner on human beings in 1900. The discovery of serological species specificities caused him to wonder if similar species differences, presumably of a minor order, existed between individuals of the same species. He chose the simplest possible method of investigation, mixing the serum of one normal individual with the red blood cells of other normal individuals. Instead of the minor reaction which he expected he found that in certain cases a marked agglutination of the red blood cells resulted while in other cases the red blood cells were entirely unaffected. On the basis of the isoagglutination reaction Landsteiner divided human beings into three distinct groups (5). The fourth and rarest group was discovered by von Decastello and Sturli in 1902 (16).

In 1911 von Dungen and Harszfeld (17) discovered the existence of sub-divisions in two of the four human blood groups and in 1927 Landsteiner and Levine (7) discovered three additional individual properties in human blood, M, N, and P. Further serological differences have been discovered and of these the Rh factor of Landsteiner and Wiener (12) seems to have the greatest clinical significance.

The serological differences in blood cells are constitutional in nature. They are determined solely by heredity, are not influenced by environment, and are inherted according to the Mendelian Laws.

The constitutional nature of the individual differences of the blood has been emphasized by the discovery that the substances which characterize the four blood groups are present in almost every tissue of the body and in most individuals also in the body fluids and secretions. There are two groups of people, the so-called "secretors" who secrete large amounts of group specific substances into the saliva and gastric juice and the "non-secretors" who fail to secrete group specific substances. The capacity to secrete group specific substances is apparently also inherited according to the Mendelian Laws. Approximately two-thirds of the people are "secretors" and one-third are "non-secretors".

Landsteiner postulated the existence of two specific substances in the serum which he called iso-agglutinins and two specific substances in the corpuscles which he termed iso-agglutinogens. The former are represented by alpha and beta and the latter by capital A and capital B. A given serum might contatin one, both or neither iso-agglutinin. Similarly the corpuscles may contain one, both or neither agglutinogen. In order for agglutination to occur when two bloods are mixed alpha must be present with A or beta with B. If small o is used to represent the absence of the two iso-agglutinins and capital O the absence of the two iso-agglutinogens then the four groups may be designated as follows:

TABLE I (1)

CLASSIFICATION OF THE BLOOD GROUPS.

Group	Cells contain iso-agglutinogens	Serum contains isoagglutinins
O	o (neither)	α & β
A	A	β
B	B	α
AB	A & B	o (neither)

The existence of subgroups in groups A and AB depends on the fact that agglutinogen A is not a single substance but includes two main sorts of properties called A-1 and A-2, therefore, there are two types of A and AB blood depending on whether the A agglutinogen is A-1 or A-2. The serums of B and O individuals contain agglutinins that react specifically with the agglutinogen A. It has been found that the so-called alpha agglutinin is composed of qualitatively different fractions of which there are two main

*All figures and tables from A. S. Wiener, Blood Groups and Transfusion, Charles C. Thomas, Springfield, Illinois, 1943, pp. XIX-438.

varieties (1) anti-A agglutinin proper reacting with both agglutinogens A-1 and A-2 with approximately equal intensity and (2) agglutinin anti-A-1 or alpha-1 which reacts with agglutinogen A-1 but practically not at all with agglutinogen A-2.

There are two theories concerning the nature of the difference between the cells of subgroups A-1 and A-2. One view, held by Landsteiner and Levine, (6) (13), maintains the existence of two qualitatively different agglutinogens A-1 and A-2. The other is that A-2 blood has a single agglutinogen A while A-1 blood has an additional agglutinogen AA-1. However, other investigators believe that the difference between the subgroups is merely quantitative, that is, caused by different amounts of the same agglutinogen in the erythrocytes. The experimental evidence seems to indicate that the difference is qualitative.

About ten years ago several workers independently reported the occurrence of individuals of group A whose blood gave only feeble reactions even with the most potent anti-A serum. The weak activity of such blood has been attributed to a third sort of A agglutinogen called A-3 (3). The discovery of this new agglutinogen brought about the recognition of two new subgroups in group A and in group AB.

Many unsuccessful attempts have been made to demonstrate the existence of subgroups in group B similar to those in group A. However, the existence of differences in agglutinogen B is not at all improbable.

In 1927 Landsteiner and Levine (7) (8) observed that when certain immune sera from rabbits which had been injected with human blood were exhausted with certain samples of human blood they still contatined agglutinins acting on the majority of blood samples of all four groups, while other bloods were not agglutinated. Two of the factors thus demonstrated were named M and N. These authors found that according to their content of agglutinogens M and N three distinct types of human blood could be distinguished; type M (blood possessing agglutinogens M but not agglutinogen N), Type N having N but lacking M and type MN having both M and N. Not a single blood was found lacking both agglutinogens. The distribution of the three types is the same in each of the four blood groups, therefore, the agglutinogens M and N are unrelated to the agglutinogens A and B.

The sensitivity of the M and N agglutinogens in the blood of newborns is equal to that of adult blood indicating that the M-N properties are fully developed at birth. These blood types remain constant throughout life. It has been found that the distribution of M and N is independent of sex since the frequencies of the three types is the same in the two sexes.

By immunizing rabbits with Rhesus monkey blood Landsteiner and Wiener (12) obtained an immune serum with which an a agglutinogen in human blood different from A, B, M, N, or P was determined. This factor was called Rh because of the use of Rhesus blood in producing the serum. About 85% of white individuals are Rh positive. This Rh factor is independent of the blood group and the M-N type. It has been demonstrated that the Rh factor is important as a cause of hemolytic transfusion reactions and plays an important role in the pathogenesis of erythroblastosis fetalis.

The Rh factor is inherited as a simple Mendelian dominant and is neither sex-linked or sex-influenced in its hereditary transmission. It also seems certain that the Rh type is fully developed at birth and remains constant throughout life.

The Rn positive type has been found to consist of different sub-types as shown in table 2.

When Landsteiner and Levine discovered the M and N factors (8) they found still another property of human blood which they called agglutinogen P. This P factor seems to be inherited as a Mendelain dominant. They believe that the so-called property P is not a single entity but comprises a group of agglutinogens similar to the A and Rh properties. It is possible, on the basis of the intensity of reaction to anti-P sera, to divide human blood into three classes. These classifications are strong, moderate and completely negative.

There is a possibility that factor P may on rare occasions cause hemolytic transfusion reactions because of the development of iso-antibodies in normal human sera and, rarely, as a result of iso-immunization in patients receiving repeated transfusions.

The so-called agglutinogen Q is unrelated to A, B, M, N, but there is a marked correlation between it and P and it is most likely one variety of the agglutinogens P. Investigators have shown that the property is inherited as a simple Mendelian dominant.

TABLE II (18)
RELATIONSHIP BETWEEN THE REACTIONS OF DIFFERENT TYPES OF ANTI-Rh SERA

Anti-Rh Sera	Originally described by	Designation of Agglutinins in Serum	Apprx. % +Reaction	Reaction of various bloods among whites 70%	15%	2%	13%
Type 1 (Standard Anti-Rh)	Landsteiner & Wiener	Anti-Rh_1	85	+	+	—	—
Type 2	Wiener & Landsteiner	Anti-Rh_2	72	+	—	+	—
Type 3	Landsteiner Burnham Katzin & Vogel	Anti-Rh_{12}	87	+	+	+	—
So-called Anti-Hr Serum	Landsteiner Javert Katzin	Anti-Hr	—	—	+	—	+

By means of the five agglutinogens, A-1, A-2, B, M and N and the two common varieties of the anti-Rh agglutinins seventy-two different types of human blood can readily be identified. This does not take into account rare bloods of sub-group A-3, A-3B, etc.

There is evidence for the existence of still other specific agglutinogens in human red blood cells. Since each additional independent agglutinogen doubles the number of sub-divisions of human blood it is possible that there might be an individuality of the blood similar to that of fingerprints. Landsteiner and Levine (10) performed an interesting experiment in this connection. The bloods of nine individuals working in their Laboratory were tested by means of immune agglutinins and certain atypical human agglutinins. When a second set of specimens labelled by number only was tested with the same reagents, it was not difficult to determine to which individual each of the specimens belonged.

However, this fine differentiation of human blood samples is not possible in general practice because of the difficulty of preparing or securing the proper reagents.

The manner in which the distribution of the various blood groups came about is unknown. There are several theories, none of which is firmly established. Some of these theories are: 1) The predominance of group O in practically all races and its occurrence practically pure in the American Indian is evidence that in man only the property O existed originally and that properties A and B appeared at a later date by mutation. Objections to this theory have been raised because of the occurrence of agglutinogens A and B in the anthropoid apes. It may be that the mutations arose independently in man and in the apes. The fact that A and B are practically absent in most Indian races would suggest that the separation of these races from the main Asiatic trunk occurred before the appearance of agglutinogens A and B. This theory, however, must be modified because as many as 75% of the Blackfeet and Blood Indians belong to group A. 2) The predominance of factor A in western Europe has been considered as indication that the factor first appeared there and spread eastward and similarly the predominance of B among Asiatic peoples has been considered evidence of the origin of B in Asia. 3) Some workers have suggested that there was not a single O race but that there were three or more races in which genes o, a, and b predominated. Their present distribution is believed to be due to migration and crossing of the original races.

Attempts to produce sera which would serve to differentiate bloods of different races particularly in the human species have been unsuccessful. Agglutinogens of human blood so far discovered are not restricted to any race and therefore the presence or absence of any in a given blood specimen cannot be used as evidence that the blood came from an individual of any given race. However, study of agglutinogens in bloods of large groups of individuals has shown that

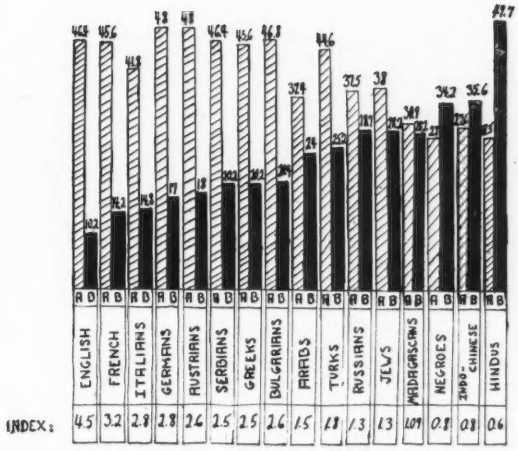

Fig. 1—Distribution of the Agglutinogens A and B. (After H. and L. Hirszfeld.)

their frequency distribution varies in different races.

The first studies on racial distribution of blood groups were made by L. and H. Hirszfeld (4) during World War I. These men were army physicians and had the opportunity to test blood samples of soldiers and civilians of different races concentrated in the Balkans. They examined five hundred to one thousand individuals of each nationality and found that the frequencies of the four groups varied in the different peoples and were related to a certain extent, to the geographic location of the countries.

The frequency of agglutinogen A decreases from west to east while the frequency of B increases. The ratio of A to B is called the Biochemical Index and is calculated by dividing the sum of the frequencies of groups A and AB by the corresponding sum for groups A and AB.

$$I = \frac{A + AB}{B + AB}$$

On this basis three types are distinguished: a European type with an index of 2.5 or more, an intermediate type with an index of 1.3 to 1.8 and an asio-african type with an index of 1.0 or less (4). The biochemical race index of the Hirszfeld's would not differentiate two races having the same relative frequency of the factors A and B although the frequency of the four groups differed widely in the two races. Figure 1.

During the past two decades hundreds of studies have been made on the distribution of the blood groups in practically every race in the world, and have been reviewed recently by Wiener in his *Blood Groups and Transfusions.*

An excellent way of showing the relation of the various races to one another with respect to the blood groups is to plot the frequencies of genes on a graph using the symbols p, q, and r to indicate the frequencies of genes A, B, and O respectively. Obviously p plus q plus r equals one and only two of the frequencies need be plotted.

Another method is the well known Streng triangle which applies the theorem that in an

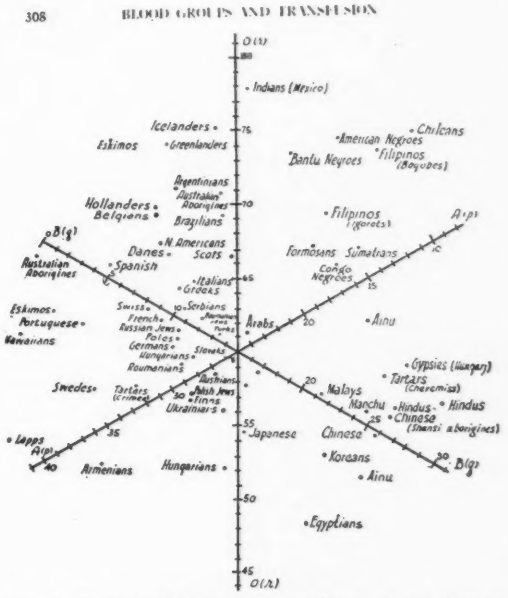

Fig. 2—Serological Composition of Many of the Peoples of the World. (Represented by means of Triangular Co-ordinates.)

equilateral triangle the sum of the distances of any point within the triangle from the three sides is equal to the altitude. If the length of the altitude is taken to equal 100% and the three distances p, q, and r respectively then p plus q plus r equal one or 100%. The triangle has the advantage that the frequency of all three genes are represented. The theorem upon which the Streng method is proved is as follows:

If AB, BC, and CA are the sides of an equilateral triangle and if the sines of the angles, which are, of course, each equal to sixty degrees, are represented by s then since the altitude is taken equal in length to unity

ABs = BCs = ACs = 1

through F draw line DE parallel to BC then triangle DEA is an equilateral triangle.

Draw DG perpendicular to BC

then DG + p = CDs

q = DFs

and r = EFS

q+r=(DF+FE)s=DEs=DAs and

q+q+r=(CD+DA)s=ACs so that p+q+r=1 (18)

When the serological composition is represented by means of triangular coordinates the point on the line represents the frequency of the blood group in the race under consideration. (18)

A convenient way of summarizing the results of the blood group investigations is to plot the data on maps. Figures 4, 5 and 6. As shown on such maps group A decreases from West to East and seldom becomes rare, group B decreases from East to West and becomes quite rare among Western peoples. There is also a second point of maximum frequency for factor A in southern Korea and Japan. The relative rarity of mutation B may be due to its more recent appearance or to its having occurred originally in fewer people. Or there may have been an independent mutation of A occurring in Asia. There are two possibilities: 1) the blood groups are older than the present races and 2) the blood groups arose at a later period in man's development. Those who favor (1) say that when few men existed and groups A, B, and O were to be found chance governed the formation of families with different blood groups giving rise to certain primitive stocks each belonging to one or another of the groups. This explains the blood similarity of geographically separated peoples, e.g. Greenlanders and Australians, the Chinese of Canton and the Negroes of the South Belgian Congo. The evidence against (2) is mainly that it presupposes too high a rate of mutation.

Eighty percent of white individuals of the United States and England who belong to groups A and AB are A-1 or A-1B. Among the negroes in New York City the incidence of A-2 and A-2B is higher than among the whites. In pure Hawaiians with 60.8% of their population belonging to group A all those of group A who were examined in a study made by Nigg were found to be A-1. The same situation is found among full-blooded Indians.

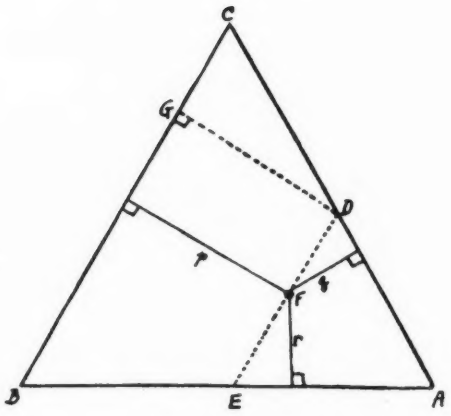

Fig. 3—Streng's Triangle

Many races thus far examined have the same or similar distribution of M and N. Striking exceptions are the American Indian, Eskimos, Hindus, Beduin, Australian Aborigines and the Ainu of Japan. Less striking differences are also found among the Finns and the Swedes. A similar prevalence of the N type has been found among the Ainu and Australian Aborigines and is explained by assuming close relationship between the origins of these peoples. In contrast is the prevalence of the M factor in the Eskimo and the American Indian. In determining the frequency of the genes only the frequency of one need be known since m plus n equals one.

Among New York Negroes the incidence of the Rh negative type is lower than in a similar white population. Among the American Indians Rh negative type appears to be practically absent. Extension of studies to other races should yield results of significance from the standpoint of

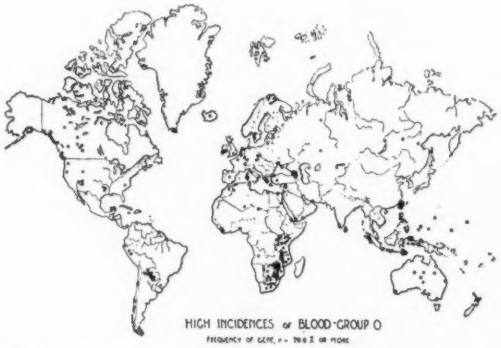

Fig. 4—Geographical Distribution of the Blood-Group Genes (after Candelia). Each dot represents the result of a separate investigation.

racial origins. A study of anti Rh-1 and anti Rh-2 types yielded the following results. (14)

TABLE III (14)

A STUDY OF ANTI-Rh_1 + ANTI-Rh_2 TYPES

Race Studied	Number Tested	%+	%—
Anti-Rh_1			
White	334	85	15
Colored	264	95.5	4.5
Colored	113	92	8
American Indian	120	92.2	0.8
Chinese	150	99.3	0.7
Anti-Rh_2			
White	334	73	27
Colored	118	46	54
American Indian	69	58	42
Chinese	150	93	7

Few studies on the distribution of factor P have been carried out because of the lack of suitable testing reagents. European whites are found to be 24% negative and 76% positive. (2) The incident of P is much higher in Negroes than in whites in New York City. (9) (11).

Few studies on the incidence of the secretor type have been carried out but significant differences seem to exist among the distributions in different populations. In Europe and the United States 80% of the population is positive and 20% is negative. The percentage of positive individuals is slightly higher in Finland and markedly lower among Negroes. (18)

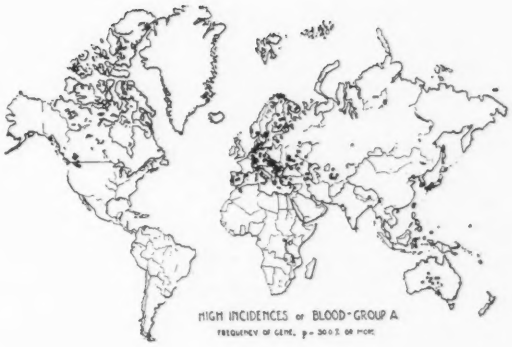

Figure 5.

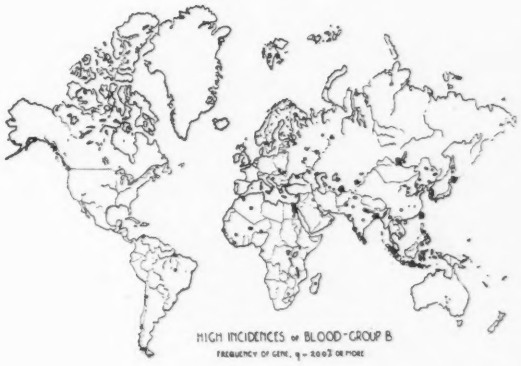

Figure 6.

Blood tests, like other anthropological criteria, may be applied either to individuals or to groups of peoples. Its application to individuals is extremely limited, however, since representatives

TABLE IV (18)

STUDIES ON THE DISTRIBUTION OF THE SECRETOR TYPE

Nationality	Investigator	Number of Persons tested	Distribution of Types S	Distribution of Types s	Frequencies of Genes S	Frequencies of Genes s
Denmark	Hartmann	100	74.0	26.0	49.0	51.0
Finland	Putkonen	197	86.3	13.7	63.0	37.0
Germany, Berlin	Schiff	363	78.0	22.0	53.2	46.8
Japan	Suzuki	424	75.7	24.3	50.7	49.3
Japan Nagasaki	Isizawa, Nonaka, Okajima and Sekimata	254	79.5	20.5	54.8	45.2
Poland	Morzycki	88	79.4	21.6	53.5	46.5
U.S.A., N.Y. (Whites)	Schiff	74	82.4	17.6	58.0	42.0
U.S.A., N.Y. (Whites)	Wiener	130	82.0	18.0	57.6	42.4
U.S.A., N.Y. (Negroes)	Schiff	178	61.2	38.8	37.7	62.3

of all four groups, all three M-N types, etc. occur in almost every race, so that the tests can be used only in a few exceptional instances; e.g. the occurrence of group B or subgroup A-2 would render it highly improbable that a given individual is a full-blooded Polynesian or North American Indian. When dealing with individuals from mixed populations, even this extremely limited application cannot be made. On the other hand, certain external traits such as skin color, type of hair, the Mongolian epicanthus etc., tend to be more uniform in people of a common stock, and collectively usually indicate quite definitely the racial derivation of the individual. The homogeniety with regard to external characters is due to intermarriage between individuals of similar racial type, while selection does not operate in the case of the blood group factors.

Nevertheless, blood grouping tests have proved to be of value for studying racial relationships and tracing racial origins. The blood tests do have limitations because peoples of the same race may have widely different distributions, while totally unrelated races may have a similar serological constitution. However, these same limitations also apply to other anthropological criteria such as the shape of the head, stature, etc. Moreover, the blood tests have advantages over some other anthropological methods in common use. Firstly the blood of every individual can be readily and accurately classified. Errors in technique can and have been made but with the aid of formulae such as p plus q plus r equal one and m plus n equal one, reports containing such mistakes can usually be recognized. Moreover, the blood group can be diagnosed reliably at birth, even in premature infants, and it remains constant throughout life and is unaffected by environment. This is not the case with many other anthropological criteria. Secondly, the hereditary mechanism of the individual blood properties is simple and well-known, so that it is possible to predict accurately the result of any racial cross when the distribution of the blood properties in the parent populations are known. In this way it is possible to test theories concerning the racial deviations of blood groups of various populations. Thirdly, the fact that there is no selection of mates on the basis of blood groups causes the blood group distribution of a population to remain constant from generation to generation, in the absence of immigration and intermarriage with other races. Finally, it is true that the published data regarding the racial distribution of the blood groups probably exceeds that available for any other anthropological criterion.

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* * *

Galen spoke of death caused by joy, and in commenting on it says that the emotion of joy is much more dangerous that that of anger.

Scientists found signs of tuberculosis in mummies in the tombs of Egypt.

The now familiar phenomenon of red-green color-blindness was not discovered until 1791, *when the scientist Dalton found himself color-blind.*

Fats, more than any other food, have the ability to satisfy hunger.

ANTIRETICULAR CYTOTOXIC SERUM

(ACS of Bogomolets)*

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THE Antireticular Cytotoxic system (ACS) of Bogomolets is an antiserum prepared in goats or other animals by inoculating them with splenic and bone marrow tissue from man. These substances act as antigens. The animals will react then, by formation of antisubstances or antibodies which have a specific affinity for human bone marrow and splenic tissue. The principle involved in the use of ACS concerns its antagonistic action to the reticulo-endothelial system. Before going any further, it may be profitable to review some of the functions of the reticulo-endothelial system.

It may be remembered that this term was coined by Aschoff as a name for the reticulum cells or structural cells of the various organs and tissues of the body. At present, it is conceived that this system includes:

1. All reticulum tissues distributed throughout the body.
2. The microphages and macrophages both of the fixed variety and the mobile variety.
3. Spleen and other lymphogenous tissue.
4. Bone marrow.

The functions of the reticulo-endothelial system are manifold. Among some of the more important ones, particularly in connection with the use of ACS, may be mentioned the following:

1. Regulation of cellular nutrition: This function is carried out primarily through the position of the R-E system in the formation of the blood-parenchymal barriers.
2. Regenerative activities: This function is exemplified by the granulation tissue of repair.
3. Resistance to infection: This function is exemplified by the phagocytic action of the fixed and mobile macrophages.
4. The possible function of the spleen as an endocrine organ: There is some circumstantial evidence in this direction which we shall have to by-pass for the moment since it is not of particular concern to the principal topic of this report.

Even though one may not agree with the various theories that have been propounded concerning the functions of the R-E system, there is certainly common agreement that this system is highly important to the efficient operation of many physiologic mechanisms.

Another phase of this problem which requires some historical delving, concerns itself with the much publicized (rather satirically) attempts on the part of Elie Metchnikoff to find the secret of longevity. We all remember the stories concerning his studies of the Bulgarian peasants who lived to a ripe old age and his erroneous conclusion that this was based upon the drinking of soured milk. Most of us, however, are unaware of certain of his basic researches with what he called "cytotoxins". Actually these were antibodies produced by injecting certain cells (i.e., red blood or white blood cells) into heterogeneous animal species as antigens. This resulted in the recipient animal engendering specific antisubstances which were naturally "toxic" or destructive to the cells used as antigens. In certain of his experiments, evidence was apparent that under some conditions the cytotoxins were stimulating rather than destructive. This was particularly true with "cytotoxins" for erythrocytes and those for polymorphonuclear leukocytes. It is to be remembered that these experiments were done in the very early part of this century and technical methods were not developed to the relatively high degree that is available now. Because of technical difficulties, Metchnikoff reluctantly admitted his inability to proceed but not before he had enunciated a remarkable hypothesis—that with the aid of *small* doses of "cytotoxic" serum, it might be possible to strengthen the functions of the most valuable elements of the body and to cause a "weakening in the aggressive tendencies of the leukocytes". This hypothesis shows a groping for an elusive truth while being handicapped by a popular misconception of that time; i.e., that the leukocytes are often harmful to the body and that their activities should be curtailed. We now know that the cells of inflammation are

an extremely necessary response to foreign elements that may have gained entrance to the body.

Essentially Metchnikoff was faced with a more or less commonly observed phenomenon, that a single substance when administered to animals may be, at first or in low doses, stimulating; but later or in higher doses, may have a depressing effect. This we find to be a very common experience with many things.

As was mentioned before, Metchnikoff's chief difficulty was of a technical nature. More specifically, he was unsuccessful in developing a proper method of assaying the "cytotoxic" sera. A. A. Bogomolets began his work in 1908 and worked more or less continuously on Metchnikoff's idea for the next thirty-eight years. His first step in order to make any progress, was to find a suitable technique of titration or assay. After many attempts he found that the complement-fixation test described by Bordet and Gengou, gave satisfactory results.

Briefly we may outline the results of the work of Bogomolets and his associates with ACS as follows. The injection of ACS into human beings presents a challenge to the R-E system because it contains specifically antagonistic antisubstances. However, injection of small doses of the antigen (ACS) acts as a stimulant and evokes a response on the part of the R-E system which is more or less non-specific. Because of the non-specific character of this response, it is conceived that it will have a beneficial effect on any deleterious process which can be controlled by a favorable response of the R-E system. To cite a few examples we point to:

1. The infectious process: ACS theoretically stimulates the antibody producing organs. This holds true whether we subscribe to the theory that antibody is produced by cells of the lymphogenous series or cells of the myelogenous series.

2. The reparative process: Administration of ACS should theoretically hasten the repair of bone fractures since callus deposition is a function of osteogenic cells which are closely related to the R-E system. In another connection the cellular processes of repair are concerned in the delimitation of neoplasms either benign or malignant. It is conceived that ACS would stimulate this process if instituted early and might prolong life, in the case of malignancy, by retarding metastasis.

3. The aging process, which is visualized as an aging of the connective tissues of the body: These are in turn influenced by the R-E system. Therefore, stimulation of the R-E system by ACS should result in regeneration and, therefore, a retardation of the aging process.

The antigen used in the preparation of ACS is obtained by removing bone marrow and spleen from fresh cadavers, preferably those who have died of unnatural causes, i.e., accidents, etc. This material is ground up and strained through a mechanical tissue press and the resulting fine suspension is inoculated by orthodox methods into heterologous animals such as goats or horses. After waiting a suitable period of time serum removed from these animals contains the "cytotoxic" substances, and this serum is called ACS. The serum is titrated by complement fixation test. Titrations must be carried out accurately and frequently so that dosages used for therapeutic or preventive purposes are exact. This is necessary because excessive dosage would lead to a blocking or destruction of the R-E system rather than stimulation.

There have been a number of reports concerning the use of ACS for therapeutic purposes in the Russian literature and the results have been remarkably favorable. There has been only one report of a comprehensive nature in the American literature which concerns the preparation of the substance and its use in the treatment of experimental fractures produced in rabbits. The results of this experiment show a remarkable degree of healing in a significantly shorter time in those rabbits which received ACS as compared to those who suffered fractures and were not treated.

In conclusion it may be stated that the principle of ACS therapy is very attractive on theoretical grounds and certainly indicates further experiment to be necessary.

* * *

"The success of the physician and the surgeon lies in the pharmaceutical science since with the good selection, preparation, and mixture of the medicaments, nature is aided in order that she conquer and exterminate the diseases."

—Regulations For the Internal, Political and Economic Management of the Royal Hospitals Erected on the Island of Cuba, . . . Year of 1776.

CRYSTALLINE DIGITALIS AND TREATMENT OF THE CARDIAC PATIENT

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TREATMENT of the cardiac patient has been greatly advanced in recent years by the introduction of the crystalline glycosides of digitalis into modern therapeutics. Cardiologists have been slow in realizing the increased benefits derived from these purified products. Although Nativelle isolated digitoxin (Digitaline Nativelle) in 1869, the glycoside first gained widespread usage in recent years. The drug has attained prominence largely through the work of Gold and his co-workers, who published extensive surveys of their work. Digitoxin began to appear on the market in the past year, since in 1945 and 1946, Wyeth (Purodigin), Squibb (Digitoxin), Lilly (Crystodigin), Abbott (Digitoxin), and many other large pharmaceutical firms began to produce the drug and "detailed" it to the general practitioner. Prior to the advent of these products, the Fougera Company was the only distributor of digitoxin (Digitaline Nativelle), although Merck-Digitoxin was available for research.

It is not the intent of this article to discuss history, chemistry, pharmacology, and circulatory dynamics relative to digitalis, and thus only singular features of these new preparations will be mentioned where noteworthy. The indications for the use of crystalline digitalis are the same as with whole leaf preparation.

Digitoxin is prepared commercially from Digitalis Purpurea, although it is contained in higher percentage in Digitalis Lanata; however, Digitalis Purpurea is more plentiful and is therefore cheaper.

Since digitoxin is a crystalline product, and is weighed in milligrams in the pure state, there is no need to consider cat units or frog units in assay and dosage, for example, the digitalizing dose with the whole leaf preparation requires about 15 cat units, and the digitalizing dose with digitoxin is 3 cat units. Twenty-four hour digitalization with the whole leaf product as advised by Eggleston is difficult because the gastric irritation of the large dose necessary with this method frequently causes nausea, and the patient may vomit in the course of receiving the large dosage. If the patient does vomit, it is difficult to determine whether he has retained the whole dose, part of the dose, or none of it, and the desired result may not be achieved. The amount of digitoxin required to elicit local gastric irritation is 5-10 mg. With 24 hour digitalization with the whole leaf preparation, the patient frequently receives over 6 mg. of digitoxin. Since the total digitalization dose of pure digitoxin is 1.2 mg. for the average patient, there is much less tendency to nausea than with the whole leaf digitalis. For accurate quick digitalization with the whole leaf product, it would seem that one is limited to parenteral administration. Digitoxin is available in 0.2 mg. tablets and since the total dose for digitalization is 1.2 mg., one may give 6 of these tablets at one time to the patient. If the situation is not emergent, the dosage may be divided into two or three parts given at one or two hour intervals; however, we have used single dose digitalization in almost all cases whether they were emergent or not. The effect desired is usually attained about eleven hours after administration. The average daily dose is 0.2 mg., but some patients may require 0.1 mg. or 0.3 mg. daily, and some may even require 0.4 mg. daily. The maintenance dose should be adjusted to meet the individual's requirements. If the patient is comatose, the intravenous preparation may be used, and it is prepared in **1-cc.** ampoules with 0.2 mg. in each ampoule. Since the intravenous dose is the same as the oral dose, six ampoules are given at one time (1.2 mg.) by the intravenous route, and the effects may be noted within 6 hours. The daily maintenance dose with the intravenous preparation is 0.2 mg., and this dose may be administered either intravenously or intramuscularly, and when the patient is ready to take oral medication, the 0.2 mg. tablets are given daily as required.

Excretion of digitoxin is the slowest of all the cardiac drugs, and this property enhances the adjusting of the maintenance dose. The toxic manifestations, however, may be of longer dura-

tion with digitoxin than other cardiac drugs due to the slow excretion of the former. Our experience has shown that the oral preparations of digitoxin should not be given in full digitalizing dosage if the patient has received morphine within the preceding hour, because nausea and vomiting usually ensues. In this situation, it is advisable to use the intravenous product.

While digitoxin is a constituent of both Digitalis Purpurea and Digitalis Lanata, namely, lanatoside C and its final cleavage product, digoxin.

Lanatoside C is a crystalline derivative of Digitalis Lanata and is prepared under the trade name of Cedilanid (Sandoz). While Cedilanid is available in tablet and injectible form, the best results are obtained with intravenous injection in which the full digitalizing dose is 1.6 mg. Cedilanid is prepared in 4 cc. ampoules containing 0.2 mg. in each cc. Therefore, 2 of the 4 cc. ampoules are required for digitalization, the effects of which may be noted as early as 4 hours after the injection. Thus it is noted that this drug acts somewhat more quickly than does digitoxin which attains its effects in about 6 hours. Once digitalized, the patient may be maintained on 0.2—0.4 mg. (2—4 cc.) daily, administered by the intramuscular route. If the patient is able to receive oral medication, he may be maintained with 0.5—1.5 mg. daily. Each tablet contains 0.5 mg. of Cedilanid. The digitalizing dose of the oral preparation is 6—7 mg. Fahr and La Due have used this amount of Cedilanid in single dose digitalization, and have reported excellent results. It has been our experience, however, that the administration of such a dose of Cedilanid frequently causes nausea, and this factor may be eliminated by dividing the total dose (6—7 mg.) into 3 or more doses given at intervals of 1 to 2 hours. The effects of oral digitalization are noted in 8 to 10 hours. The daily maintenance oral dose is 0.5—1.5 mg.

Digoxin (Burroughs Welcome) is secured by hydrolysis of lanatoside C, and is its final cleavage product. The oral digitalizing dose is 1.5 mg., and may be administered in a single dose. Each tablet contains 0.25 mg. of digoxin, and six tablets are given at once with the single dose method of digitalization. The daily maintenance dose of digoxin is usually 0.25 mg., but this may vary so that some patients may require one tablet every other day, and others 2 tablets daily, and still others may require further modification of dosage. The intravenous digitalizing dose is 1—1.5 mg. The preparation for intravenous injection is supplied in 1 cc. ampoules containing 0.5 mg. of digoxin, and after diluting each ampoule with at least 10 cc. of saline, the product may be injected intravenously; the effects are usually noted within 2 hours. If the ampoules of digoxin are given undiluted, the material will cause phlebitis. The patient may be maintained with 0.25—0.50 mg. daily, given intravenously, or by deep intramuscular injection. The daily maintenance dose may be changed to the tablets by mouth as already noted, as soon as the patient is able to take oral medication.

The advantage of these new crystalline compounds over the older preparations of digitalis is quite obvious. The physician will find it simple to add these drugs to his list of cardiotonics, since the consistency of dosage contained in each tablet, and the lack of nausea, except with intoxication, makes the application of these glycosides to any patient an easy task.

* * *

Obligations of the Physician

1. The physician must visit the patient two times each day. In these ((visits)) he will take care that silence and tranquility are maintained in order that each one of those who accompany him may note without error what he orders . . .

2. He will watch to see whether the medicines are made according to the profession of which knowledge he will be instructed by the effects which they produce on the patients.

3. He will endeavor to know if the bread, meat, wine and other food have some defect which may be harmful to the patients. He will do this without making it known to the latter in order that they may not fulminate gossip.

4. He will be on good terms with the others of his faculty (if they exist) discussing the urgent cases with them . . .

5. It will not be less useful to maintain the same good harmony with the head surgeon . . .; since I have found out by experience that because of discord among the physicians the patients are sent from one to the other even though the same ailment which they had remains in them . . ."

—Regulations For the Internal, Political and Economic Management of the Royal Hospitals Erected on the Island of Cuba, . . . Year of 1776.

THE BIOCHEMICAL AND PHARMACOLOGICAL PROPERTIES AND THE CLINICAL USE OF 2.3 DIMERCAPTO PROPANOL

(British Anti-Lewisite)

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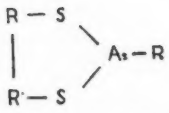
This review is based on the work done by British and American workers under contract with the Ministry of Supplies in England and the Office of Scientific Research and Development in the United States. Most of the papers referred to have been published in the Biochemical Journal 1946, **40,** 513, in the Journal of Pharmacology and Experimental Therapeutics, 1946, **87** (Supplement), 3 and in the Journal of Clinical Investigation 1946, **25,** 451. Other pertinent papers will be quoted and listed in the Bibliography.

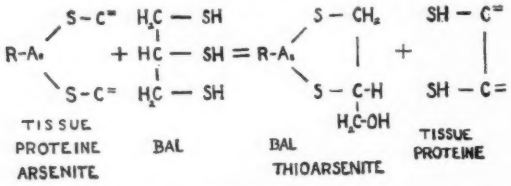
Biochemical properties of BAL

2,3-Dimercaptopropanol, or British Anti-Lewisite (BAL) as it has been called by the American workers, is a colorless liquid with a strong mercaptan odor, and a specific gravity of 1.21. It is soluble in water to a maximum of 6% and in vegetable oils. The history of our knowledge regarding BAL is extremely interesting because it is a complete story of how pure biochemical work led to the development of a substance with great practical possibilities, through a series of very logical steps. From the point of view of scientific methodology the development of BAL is similar, although on a minor scale, to that which led from the theoretical and now famous formula of Einstein to the harnessing of atomic energy. Our story begins with the early fundamental contribution of Voetglin, Dyer and Leonard who discovered, in 1923, that the trypanocydal action of arsenoxide could be reversed by certain monothiols, such as reduced glutathione and thioglycollic acid. The depressant action of arsenoxide on the respiration of mammalian tissues in vitro could also be prevented or reversed by the monothiols. This action of monothiols was not understood until Walker (1925, 1928), and Dickens (1933) discovered that arsenic, cyanide and iodoacetate, which have in common the property of inhibiting tissue respiration, combine with the sulfhydryl (SH) groups present in the tissue proteins. In 1936 Peters discovered that arsenites inhibit the oxidation of pyruvate in the brain tissue and suggested that this was due to the inactivation of the SH groups essential for the action of pyruvic acid oxidase and pyruvic acid dehydrogenase. Using arsenicals and other reagents capable of combining with the sulfhydryl groups of the protein enzymes, Barron and Singer found that the SH group is essential for the physiological activity of a large number of enzymes related to the metabolism of carbohydrates, fats and proteins. The use of these SH reagents not only provided a means for the classification of enzymes, but also led Singer and Barron to the formulation of an interesting hypothesis on the fundamental action of glutathione. The continuous production of oxidizing agents in the cell will tend to inhibit the action of the enzymes for which the SH group is essential by converting the latter to an inactive —S—S— linkage. Glutathione, which is capable of rapid oxidation and reduction, would continuously reactivate the enzymes by reducing the —S—S— groups to SH. Vitamin B1 is necessary for the action of brain pyruvic acid oxidase and, as expected, Peters and collaborators found that repeated injections of arsenicals produce in pigeons, mice and rats a chronic neuritis similar to that due to thiamine deficiency. In both cases the metabolism of pyruvic acid by the brain is inhibited.

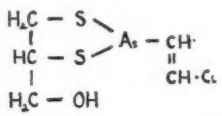
Arsenicals are used as vesicants in chemical warfare. For this reason Thompson studied the action of Lewisite on the metabolic processes of the skin and found that pyruvate oxidation could be completely inhibited in a manner very similar to that of the brain. He further found that the biochemical lesions could be demonstrated before the appearance of erythema or edema. Stocken and Thompson studied the reaction between arsenicals and a soluble protein in vitro. Using Kerateine, which contains an abundance of SH groups, the authors found that a stable linkage is formed between arsenic and SH and suggested the following formula for the arsenic-protein compound:



From this formula it is clear that protection against the action of arsenicals should be afforded by thiols containing SH groups capable of competing with the proteins for the arsenic. This is probably the explanation for the early experimental results of Voegtlin and collaborators. To test this possibility, Peters, Stocken and Thompson studied the action of various thiols on the oxygen consumption of the brain-pyruvate system. The authors found that, among the various SH containing substances studied, 2,3-dimercaptopropanol best reversed the inhibition of pyruvic acid oxidase brought about by arsenic. The phenomenon is explained by the following equation:



In the case of Lewisite the BAL compound has the following formula:



Results similar to those obtained with the brain were obtained by Stocken and Thompson studying the skin respiration in vitro. In vivo experiments showed that the inunction of the skin of rats within one half hour of the application of a lethal dose of lewisite resulted in 100% survival and that 14 out of 16 animals survived even when the antidote was applied as late as two hours of the exposure to lewisite, when local and general signs of poisoning were already well under way. If treatment is started within 5 minutes, BAL can counteract the effects of 11 times the dose of lewisite capable of killing one-half of the animals (LD50). BAL has also a preventive action which seems to last for at least 23 hours after application to the skin. The authors repeated the experiments on 4 human volunteers and found that no vesication occurred if BAL treatment was begun within 30 minutes of the exposure to lewisite.

Having determined that BAL had the property of neutralizing the toxic effects of lewisite, it was necessary to study the pharmacological properties and the toxicity of BAL itself.

Pharmacological properties and Toxicity of BAL.

Chenoweth studied the cardio-vascular action of 2,3-dimercaptopropanol in cats and found that, if injected intravenously in sufficient amounts, it produces a drop in the arterial pressure to shock levels associated with respiratory depression. The section of the vagi or atropinization did not modify the results and the electrocardiographic changes were not sufficient to explain the decrease in blood pressure on the basis of an action on the heart. A study of the peripheral, resistance revealed that BAL has a strong vasoconstrictor action on the blood vessels of the leg and does not modify the resistance of the blood vessels of the splanchnic area. The failure of the blood pressure cannot, therefore, be explained on the basis of the action of the drug on peripheral resistance. Following the injection of BAL, the blood volume decreases about 30%. This is due to a severe damaging action of the drug on the capillaries which become dilated and more permeable to blood proteins. The action of BAL was found to be independent of the nervous system. The author concludes that BAL produces a severe paralysis of the capillary bed with increased permeability and loss of plasma into the tissues and this in turn, produces a severe drop in blood pressure despite the marked vasoconstriction of the arterioles. The work of Chenoweth was confirmed by Hitchcock who perfused the hind leg of the cat and various organs of the cat and the rabbit with Ringer containing BAL. He found that the drug produces a strong vasoconstriction of the arterioles of the leg, but has no effect on those of the liver, kidney and heart. He also found that similar results could be obtained by adding other enzyme poisons to the perfusing fluid. He concludes his paper with the interesting remark that BAL is the first substance known to act directly on the blood vessels and, contrary to pituitrin, nitrites and others, have different effect on various types of arterioles. Studying the effect of BAL on the skeletal muscle, Krop found that the anaerobic processes leading to the formation of lactic acid are not impaired, but that the oxidative (delayed) heat is completely inhibited. This heat is believed to be

produced by the oxidation of lactic acid and, accordingly, lactic acid accumulates in large amounts in the liquid perfusing a muscle poisoned with BAL.

Chenoweth and collaborators studied the systemic toxicity of BAL and of several related compounds. Doses as small as 0.005cc/kg were injected intravenously into cats and were followed by blinking, lacrimation and salivation. Larger doses produced stronger and longer lasting results; among the effects were: blepharospasm, conjunctivitis, anorexia, vomiting, diarrhea, apprehension, depression, tremor, unrest, excitement, ataxia, convulsions, catatonia, shock, pulmonary edema and others. Doses of 0.03cc/kg were often fatal and death would follow a period of gasping respiration, pulmonary edema and myoclonic convulsions. The accumulation of lactic acid in the blood of the BAL-treated cats suggested to the authors the idea of injecting large doses of lactic acid intravenously. The results were similar in many respects to those obtained by the injection of BAL, but the authors feel that the increase in the concentration of lactic acid in the blood does not explain completely the action of the drug. In view of the fact that BAL was found useful in the prevention of skin burns due to lewisite, the authors investigated the toxicity of BAL when applied to the skin. The results were comparable to those obtained with the smallest intravenous doses, except when unusually large areas of the skin were painted with BAL solution, or when very large doses of the drug were used. Sulzerberger and collaborators studied the toxicity of BAL by parenteral and percutaneous administration in man. Five normal adult volunteers were studied. Three grams of BAL in the form of a 10% jelly were rubbed into the skin of the forearm and arm. In 5 other volunteers the drug was rubber into the skin of the neck, back, shoulders, arms, chest and abdomen. The local reaction ranged from none at all to severe generalized whealing of the whole area. This, however, subsided gradually and 36 hours after the application of BAL only a slight erythema remained. 34 human volunteers received intramuscular injection of BAL. A total of 4 injections at 2 to 4 hour-intervals were given over a period of 1 or 2 days. The highest single dose ranged from 5 to 6.3mg/kg and the highest total amount given was of 42mg/kg. The injection was followed by local pain lasting as long as 24 hours. Doses of 3.6mg/kg or higher produced slight headaches, nausea and burning of the mouth, reaching a maximum in about 10 to 30 minutes. Less frequently the subjects complained of conjunctivitis, tearing, rhinorrhea and salivation, of paresthesias, sweating and abdominal pain. If a second injection is given two hours after the first the symptoms are much more severe, but if an interval of 4 hours elapses, there are no signs of accumulation. The authors conclude that 4 doses of 4mg/kg of BAL at 4 hour-intervals can be safely administered to man. The same authors investigated the skin sensitization to BAL by daily applications of BAL ointment to the skin of 102 volunteers. The results indicate that a certain amount of local sensitization can be produced in 19% of the cases and that this percentage increases to 66 if the drug is applied to skin previously damaged by mustard gas. The sensitization, however, is not severe enough to constitute a contraindication for the use of BAL ointment.

Experimental Therapeutics.

The next chapter in the story of the development of BAL is that of experimental therapeutics. Harrison and collaborators studied the treatment of the systemic toxic effects of skin contamination with lewisite and phenyldichlorarsine by 2,3,-dimercaptopropanol. The arsenical was applied to the skin of mice in amounts equal to 3 LD50's and 30 minutes later the animals were treated with local application of undiluted BAL or by repeated injections of BAL in saline. The injections were found to be more effective, especially when repeated at 3 to 4 hour intervals for 12 hours. The total amount of BAL for optimal results was found to be 1mg/Kg which reduced the mortality from 100% to a minimum of 10%. When dogs were burned with 38 mg of lewisite per kilo the local treatment alone was not sufficient to save the animals from circulatory collapse and death, but a combination of local treatment and intramuscular injections was found to be very effective.

The exposure of the eyes to relatively small doses of lewisite produces devastating lesions resulting in complete necrosis of the eye bulb. The lesions are due in part to the hydrolysis of lewisite with production of hydrochloric acid, but mostly to the arsenic itself. Hughes exposed 600 rabbit eyes to lewisite by instilling 0.1 mg into the conjunctiva or by exposing the eye to

lewisite vapors for 30 minutes. He found that within 2 to 4 minutes no toxic material remained on the surface of the eye as indicated by the fact that tears could be transferred to the other eye with impunity. Lewisite had penetrated into the corneal substance and remained there for at least 1 hour, although As could be found in the aqueous humor within 1½ minutes of the application. This rapidity of diffusion explains why antidotes like saline irrigaton, iodine solution, or hydrogen peroxide have little or no effect in the treatment of lewisite injury. Fortunately BAL seems to penetrate the tissues of the eye as fast as lewisite does and does not injure the eye severely or permanently. If a 5% BAL ointment was applied to the eye within 2 minutes of the exposure to lewisite the action of the latter was completely prevented. Even if applied 30 minutes after exposure the lesions were less severe and lewisite resulted in relatively mild permanent damage.

The influence of BAL on the fate of arsenic in the body was studied by Riker and Rosenfeld. When mapharsen is injected into cats only 10% of it remains in the blood 1 hour after the injection and 5 to 6 hours afterward it had disappeared completely. If BAL is injected there is a sudden and sharp rise in the blood concentration of arsenic, indicating that it is mobilized from the tissues by the drug. The blood carries the arsenic to the kidneys, and Stocken and Thompson found that after an injection of BAL there is a sharp increase in the urinary excretion of the metal. This was found to be true in human volunteers exposed to minimal amounts of arsenical smoke in a gas chamber. Wexler and collaborators found that after repeated injection of BAL the urinary excretion of arsenic increased up to 100% with the maximum increment lasting for 2 to 4 hours after each injection. The authors suggest that for maximum detoxification BAL should be administered at 4 hour intervals. We already saw that this is also the interval suggested to avoid cumulative toxic effects of the drug.

Clinical Applications.

The biochemical, pharmacological and toxicological properties of BAL having been studied, the drug was ready for clinical trial. Eagle used it in the systemic treatment of arsenic poisoning due to intensive treatment of syphilis. BAL was injected intramuscularly as a 5% solution in benzylbenzoate and peanut oil. One injection every four hours was given the first day and the treatment was continued with one or two injections per day until satisfactory results were obtained. The report deals with 219 cases which were classified as follows: 55 cases of hemorrhagic encephalitis of which 40 had convulsions or were in coma. Of these 44 recovered and 11 died; 88 cases of arsenical dermatitis, of which 55 were of the exfoliative type. Of these 80% responded to treatment within 3 days and had recovered within 13 days, 20% did not respond, possibly because the treatment was inadequate; 11 cases of agranulocytosis with 1 death and 10 recoveries in 7 days; 3 cases of aplastic anemia who did not respond to treatment; 14 cases of jaundice of which 5 responded promptly and 9 did not; 4 cases of massive overdosage with mepharsen given by error, of these 3 recovered and 1 died; 44 cases of arsenic fever who recovered promptly. Equally encouraging results were obtained by Longcope and collaborators and by Carleton and collaborators.

The chemical properties of BAL suggested that the substance might be effective in the treatment of poisoning from heavy metals other than arsenic, as they also are believed to act mainly by combining with the SH groups of the proteins. Gilman and collaborators found that mercury reacts in vitro with BAL with formation of complexes comparable to those formed by arsenic and were able to treat successfully rabbits and dogs poisoned with mercury bichloride. The authors also found that BAL glucoside is more effective and less toxic than BAL itself. The treatment of human mercurial poisoning was attempted by Longcope and collaborators and the results were excellent. Of 44 patients who had swallowed 0.5 to 20 grams of mercury bichloride and who had been treated with 2 or 3 injections of 150mg of BAL, only 2 died. Of these 1 was the first patient on whom the treatment was tried and the other had swallowed the poison 5 to 6 hours previously. The intramuscular injection of BAL given within 4 hours of the injection of mercury bichloride had striking effects, which include a complete protection of the kidney, with negligible rise in NPN, even if the mercury had already appeared in the urine.

BAL seems to reduce the toxic effects of organic mercurial compounds. Long and Farah found that the toxicity of the mercurial diuretic Salyrgan for cats and dogs and for the heart-lung

preparation was greatly decreased by the administration of BAL.

BAL glucoside was found to be effective against cadmium intoxication by Gilman and collaborators and BAL gave encouraging results in the hands of Tobias and collaborators. Other metals were investigated: the toxicity of antimony is significantly decreased by BAL, so is that of Bismuth, Chromium, Nickel. Negative results were obtained in acute and chronic lead poisoning, in the intoxication with Thallium and Selenium (Braun and collaborators) and in chronic experimental argyrosis (Olcott and Riker).

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Social Notes

ANNOUNCEMENTS OF THINGS TO COME

Leonard M. Rothstein became engaged to Miss Marcia E. Zuriff on March 26, 1947.

Irwin Bluth became engaged to Miss Harriet Shier on December 28, 1946. Truly a famous event.

Al Norman became engaged to Miss Muriel Zan on February 22, 1947. A perfect date to announce a proposed union!

Edward R. Svetkey became engaged to Miss Marcia Tuchman on October 20, 1946.

Melvin Goldy became engaged to Miss Florence Burstein on January 24, 1947. To leave no doubts, they will be married on June 22, 1947.

Theodore Cohen became engaged to Miss Barbara Ann Zweig on December 25, 1946. That's real Christmas spirit, Teddy; and to one of Brooklyn's prettiest!

FINAL DECREES

Howard Raubitschek was married to Miss Elaine Lesserman on February 22, 1947 at the Standard Club in Chicago.

Abraham S. Rosenstein and Miss Ruth F. Tanenhaus will be married on June 28, 1947 in Binghamton, New York.

Adrian Gasior and Miss Virginia Russell will be married in June in Chicago.

Michael Pavlo and Miss Rita Kund will be married some time this summer.

Wayne Hilton and Miss Sylvia Sanders will be married on July 27, 1947.

Irwin S. Morse and Miss Sally Watman were married on April 3, 1947.

TRIED AND TRUE

Mr. and Mrs. Seymour Werthamer will celebrate their third wedding anniversary on June 17, 1947. Mrs. W. warns the fledglings above about the trials and tribulations of being the wife of a Medical Student.

Mr. and Mrs. L. W. Tannenbaum will celebrate their 2nd wedding anniversary on June 20.

Mr. and Mrs. John J. Mera will celebrate their sixth wedding anniversary on July 22, 1947.

Mr. and Mrs. A. H. Rothenberg celebrated their 1st wedding anniversary on May 18

AMBITION

Mrs. Narissa P. Singh, a member of the Sophomore Class, received the degree of Master of Science in Public Health from Loyola University.

New Members of the Phi Lambda Kappa Alpha Rho Chapter

Altman, Sheldon G.	Matanky, Seymour Robt.
Berson, Harold E.	Miller, Milton
Brown, Harold Nathan	Packer, Marvin Sam
Cohen, Norman F.	Rosenfeld, Bernard D.
Ehrich, Melvin	Rosenstein, Abraham S.
Elegant, Lawrence D.	Rubin, William H.
Epstein, Arthur	Sandberg, Herschel
Fishbein, Herbert L.	Schaefer, Gerschen L.
Milton, Wayne	Schlansky, Seymour M.
Kantor, Nathan I.	Schumer, William
Katz, David	Shaw, Morton A.
Libert, Samuel A.	Sherman, Jr., Maurice J.
Lieberman, Murray	

Officers of Alpha Rho

Worthy Superior.....Jerome A. Ehrlich
Worthy Chancelor.....William C. Feldman
Worthy Guardian of the Exchequer—
Myron Saline
Worthy Scribe.....Robert R. Simner
Alumni Scribe.....Bernard Kleppell
Sergeant-at-Arms .....Jerome Zwanger

CLINICAL REPORT OF CUTANEOUS BLASTOMYCOSIS

David M. Cohen, M.D.
Associate Professor of Dermatology
The Chicago Medical School

WE WHO live and practice in the great middle west of the United States, especially around Chicago must be on the constant alert for Blastomycoses infections. This deep fungus infection although not very common is one of vital importance. Because of its potentially invasive character the entire body may be involved. Therefore, lack of recognition and delay in beginning treatment may result in a fatal outcome. These patients may be seen by general practioners, internists, surgeons or other specialists as well as dermatologists and, therefore, the diagnostic possibilities of fungus disease should always be kept in mind by all.

Report of a Case

Mr. J. R., a white man of 60 years of age, who has been a street car motorman for many years, was referred to our clinic by a staff member (Dr. J. G.) on August 22, 1946. His complaint was the presence of a large granulomatous patch on the right forearm of seven months duration. The patent developed a small lesion on the lateral surface of the right forearm seven months ago. This lesion began to enlarge and ulcerate. At no time was there any marked pain, tenderness or fever associated with this. Previous treatment had consisted of the local application of boric acid packs, boric acid ointment and alcohol. Sulfadiazine had been given internally. There was no improvement in his case up until the time he entered the clinic.

Physical examination was essentially negative except for his skin condition. On the extensor surface of the right forearm below the elbow a single lesion was present the size of a man's palm. The area was sharply demarcated from the normal skin. The margins were distinctly elevated with papillary projections and at the base pustules were present. Some of these were open and others unopened. Pressure upon the borders of this patch resulted in pus appearing on the surface. The center of the patch was partially crusted with some granulation tissue.

Laboratory Data revealed negative serology, blood count normal, blood sugar 228 mg/%. Urine 4+ sugar.

Biopsy of the edge of the lesion revealed a marked acanthosis which was quite irregular and had a rudimentary hornification in many of the deeper pegs. Scattered throughout the deeper pegs were numerous intraepithelial abscesses with many leucocytes, many histocytes and a few giant cells. In several of these abscesses there were double contoured bodies typical of blastomycoses. In the cutis especially about the pegs there was a granuloma with many plasma cells and a number of giant cells. A diagnosis of cutaneous blastomycosis and diabetis mellitus was made.

The patient was placed on diabetic management and on September 10, 1946, treatment for his skin lesion was started and a solution of potassium iodide 10 gms. in 180 cc. of water was begun. He began with one tablespoon daily and this was increased to five tablespoonfuls a day. Boric acid ointment was given locally On September 17th the lesions began to show improvement. The borders were less raised and within another period of two weeks the borders began to flatten out. The follicular element was practically healed. At this time the patient developed an iodide acne. From October 8th to October 29th the improvement continued until an eczematous reaction developed. Many oozing follicular areas developed. The boric acid ointment was discontinued and 2% resorcin compresses were given. Within two weeks all the eczematous reaction had disappeared. On November 26th a fine shiny scare covered with scales was seen in the center of the area. The periphery still had some elevation. On December 3rd the patient was so improved that he discontinued wearing any bandage. This improvement continued up until February 1947 when all medication was stopped. In March the patient was discharged from active attendance at our clinic with instructions to report at monthly in-

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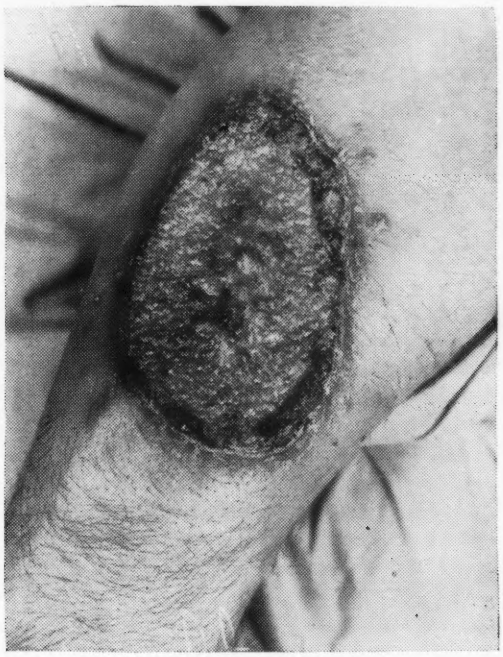
From the Chicago Medical School Clinic.
Department of Dermatology and Syphilology of The Chicago Medical School.
Dr. M. Oppenheim, Chairman.

tervals. The patient's response to the diabetic management was excellent. At the onset he was given 20 units of insulin, twice a day. After several weeks this was discontinued and now the patient's urine is sugar free and he is on a 2200 calory diet.



Before Treatment

Discussion

In typical cases of cutaneous blastomycosis of the North American type the eruption may appear as a single lesion. After a time, however, in about half of the cases more than one lesion appears. The sites involved are mainly on the exposed parts of the body, as the face, hands and wrists, but no portion is exempt. The condition is an extremely chronic one if untreated. The subjective symptoms are as a rule slight or absent except when secondary infection results in a more acute inflammation.

The primary lesion is a papule or a pustule which early becomes covered with a crust. This lesion enlarges slowly by peripheral extension to form a plaque. Although the process is usually a very slow one, lesions may get to be the size of a man's palm or even larger. A typical lesion appears to consist of a patch which is elevated from the skin, its surface is covered by a crust with papillary elevations which impart the aspect of a verrucous or cauliflower lesion. The border slopes abruptly from the verrucous surface to the normal skin from which it is sharply defined. It is smooth, dark red to purplish red in color, and on close inspection it seems to contain a large number of minute abscesses. Most of these abscesses are microscopic but others reach the size of pinheads and can be seen with a hand lens. Some of the abscesses are superficial, many are deep-seated. When they are punctured with a needle, a thick glair or muco-pus is obtained.

As the lesion enlarges the center may undergo spontaneous healing and form a scar. The scar is soft, pinkish white in color and has only a slight tendency to contracture. It is not uncommon to see areas that have apparently healed, again be infected with active foci of the disease.

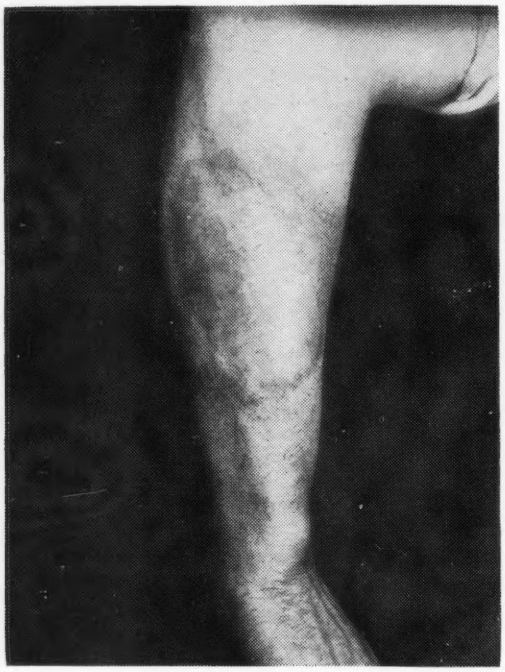
Examination of the contents of the unopened abscesses may reveal the presence of the causative organism, the Blastomycoses dermatitides. It appears either as a single or a budding spherical cell 8 to 15 microns in diameter with a thick refractile wall. No mycelium are present. Cultures of this pus on Sabouraud's glucose agar slant incubated at room temperature will reveal a white cottony aerial growth. This later becomes brown or tan. When first cultured the growth remains yeast-like and later there is an overgrowth with white aerial mycelium. The culture can also be grown at 37°C on blood agar and the microscopic examination will show a colony of budding yeast-like cells.

Aanimal innoculation into white mice gives positive results and the production of granulomatous nodules in the skin, lungs, kidneys and other organs from which it is possible to culture the organism.

Histological examination of the edge of a lesion of cutaneous blastomycosis shows the epidermis to be hypertrophic. The rete are acanthotic and form marked downward prolongations. This at times reaches a degree which is referred to as pseudo-epitheliomatous hyperplasia. There are many polymorphonuclear leucocytes throughout the epidermis and dermis. It is about these collections of leucocytes that the miliary abscesses are formed. The dermis shows cellular infiltrations with polymorphonuclear leucocytes, epithelioid plasma, and giant cells. Granulomata re-

sembling miliary tubercules may be present especially in the deeper part of the corium. Within the giant cells the B. dermatitides parasite may be present. In the miliary abscesses the parasite may be present or lie loosely in the granulation tissue. The number of organisms present may vary from a few to enormous numbers.

The differential diagnosis of cutaneous blastomycosis includes verrucous tuberculosis, vegetative drug eruptions such as ioderma and bromoderma, epithelioma, late syphilis and other granulomata. The similarity to tuberculosis verrucosa is sometimes so close that it is impossible to differentiate the two diseases by clinical examinations without resorting to laboratory procedures. However, the course of blastomycosis is



After Treatment

much more rapid and the involvement is much more extensive. The keratinizing character of verrucous tuberculosis is not seen in blastomycosis which presents an extremely fine, soft, verrucous lesion. There is a lack of the sharply sloping border with its miliary abscesses. Ioderma and bromoderma develop much more rapidly than does blastomycosis and are generally more acutely inflammatory and less purulent. This together with the history of ingesting a drug and clinical examination of the urine aid in establishing a diagnosis. Epithelioma develop much more slowly, are more infiltrated and do not contain any pustules. In syphilis the gummatous lesions do not have the red and violaceous halo, have a tendency toward ulceration, are characteristically arciform and reniform in arrangement. There are no miliary abscesses. The serology is usually positive.

The prognosis of cutaneous blastomycosis is usually favorable if a diagnosis is made early. Even in neglected cases if the lesions remain localized the response to treatment may be good. If dissemination takes place, and no one can determine whether the disease will be systemic, the outlook is poor. About 90% of the disseminated cases end fatally.

In the treatment of cutaneous blastomycosis iodides head the list of therapeutic measures. If the disease is confined to the skin it may be expected to clear completely in a high percentage of cases. This is not always the case. Iodides are given internally as a solution of Potassium iodide. The dose varies up to 6½ to 13 grains or more per day depending upon the patient's tolerance. The amount and the duration of administration of the drug depends upon the clinical response. Iodine can also be given intravenously in the form of Lugal's solution.

If the lesions are small and easily accessible surgical excision is an excellent way of eradicating the disease. Filtered roentgen therapy can be given as an adjuvant to other forms of therapy. Other methods employed consist of fever therapy, arsphenamine and colloidal copper injections, vaccine and filtrates but these have not met with general success. Local treatment consists of the use of cleansing or antiseptic lotions or ointments.

Conclusion

A sixty year old man who had cutaneous blastomycosis of seven months duration was treated with an iodide solution internally. After seven months of treatment, an apparent cure was obtained.

* * *

"One cannot practice medicine alone, and practice it early and late, as so many of us have to do, and hope to escape the malign influences of routine life." —Sir William Osler

Faculty Notes

We regret to announce the recent illness of Dr. Peter Gaberman. He suffered a coronary attack in April and is recuperating at the Mount Sinai Hospital. His quick recovery is the hope of the entire student body and staff of C.M.S.

Dr. Maurice Oppenheim at the annual meeting of the "Gesellschaft der Aerzte in Wien," January 1947, was unanimously elected an honorary member.

The following attending physicians at the Cook County Hospitals are on the staff of The Chicago Medical School:

Drs. Borovsky and Aries—Pediatrics.
Drs. Taub and Gaberman—Medicine.
Dr. Rosenblum—Medical consultant in G. U. Surgery.
Dr. Miller—Orthopedic Surgery.
Dr. Garner—Neurology.
Drs. Fischmann and W. Reich—Gynecology.
Dr. Kirshbaum—Pathology.
Dr. Christofferson—Surgery.

NEW MEMBERS OF STAFF

Dr. Donald S. Miller—Attending Physician at C.C.H. in Orthopedic Surgery, and head of the Department of Orthopedics and Traumatic Surgery of The Chicago Medical School.

Dr. H. H. Garner—Attending Physician at C.C.H. in Neurology and head of the department of Neurology and Psychiatry of The Chicago Medical School.

* * * * *

It is often a mark of brilliance when a man as young as Dr. Harry H. Garner is appointed to the chairmanship of the department of his field in a medical school. It is, as well, a credit to the growing staff of The Chicago Medical School that Dr. Garner has accepted the post of head of the Department of Neuropsychiatry, and it is with understandable pride that the Quarterly welcomes him to the rostra of our faculty.

A native of Chicago, Dr. Garner received his B.S. and M.D. degrees from the University of Illinois in his early twenties, and then completed a two year interneship at Cook County Hospital in 1936. Early in his medical career he became interested in psychiatry, and as a result served in the United States Army in the recent war as Division Psychiatrist for the 26th Division. Dr. Garner spent considerable time in the European Theater where he was exposed to the various neuroses and psychoses in servicemen which develop under the stress of actual combat, and was able to study clinically the new developments in the treatment of these conditions. His previous training made him especially capable for such a position for following his interneship, he took post-graduate work at Elgin State Hospital, Illinois Psychiatric and Chicago Research Hospitals.

Dr. Harry H. Garner

In 1940 he became a member of the American Boards of Psychiatry, and in 1942 a member of the American Boards of Neurology. He is affiliated with Mt. Sinai Hospital, is a member of the attending staff in neurology at Cook County Hospital, and is Chief of the Neuropsychiatric Branch of the 7th Veteran's Administration Division, including States of Illinois, Indiana, and Wisconsin. Also Dr. Garner is a Fellow of the American Psychiatric Association, a member of the Illinois Psychiatric Society, the Chicago, the Illinois, and the American Medical Associations. In addition to this background, Dr. Garner has

had teaching experience at the Rush Medical College from 1937-38 as Clinical Associate in Neurology, at the University of Illinois Medical School from 1939-44 as Clinical Associate in Neurology, and in 1945 at the same school as Assistant Professor of Psychiatry.

Dr. Garner has been an active contributor to neuro-psychiatric journals, having done considerable research in various phases of his field. Today, with the increased recognition of the importance of psychosomatic medicine and the realization of the frequency with which it must be dealt in clinical medicine, it is understandable that Dr. Garner's post is an extremely important one.

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Alumni News

DECEASED

Dr. Thomas F. Walsh of Chicago—Died Sept. 14, 1946 at the age of 57. He graduated from the Chicago Medical School in the year 1917 and enjoyed 30 years of successful practice.

1936—Dr. Carlo Joseph Panzarella—"country Doctor"—has a ten room clinic where he performs minor surgery. Outside activities are fishing, raising rabbits, chickens, and has wonderful garden which occupies quite a bit of his time.

1937—Dr. A. I. Podolsky, while in Chicago taking a post-graduate course in Pediatrics, visited the school. He will present a paper at the meeting of the Arizona State Medical Association on "The Treatment of the Dehydration of Diarrheas in Infants," in May.

1938—Dr. Alfred F. Akkerson is now in general practice. He is on the attending staff of the MacNeal Memorial Hospital in Berwyn, Ill., and the West Lake Hospital in Melrose Park, Ill. He is also the Medical Director, Baptist Home & Hospital, Maywood, Ill.

Dr. John Jacob was licensed in Ohio in 1946. He served in 116th Evacuation Hospital as a General Surgeon—was awarded the bronze star. Dr. Jacob is now specializing in surgery and obstetrics.

Dr. George E. Fisher is now located at the O'Reilly Veterans' Hospital, Springfield, Missouri. He is licensed to practice in Mass., Ill. and N. Y.

1939—Dr. Norman W. Jonas served 45 months as a Commissioned Medic in the U. S. Army. He is at present a resident physician of tuberculosis at the Barnstable County Sanatorium.

Dr. H. I. Blumenfeld has been elected secretary of the Brooklyn Medical Chapter of the American Veterans' Committee.

1940—Dr. Adio A. Freeman has been named Director of the Mental Hygiene Clinic, V.A., State of Iowa. He was formerly a Fellow in Psychiatry at the Menninger Clinic, Attending Psychiatrist at the Winter, General Hospital, and Lt. Col. Mc. Res. A. U. S.

Dr. K F. Kapov is now in General Medicine. He is Assistant Physician and Surgeon of The Armour Co.

Dr. Samuel R. Coleman is at present located at 184-20 90th Ave., Hollis 7, L. I., New York.

Dr. Sam S. Cooper announced the opening of his office for General Practice and Surgery at 404A West Fifteenth St., Austin, Texas.

Dr. and Mrs. L. M. Hart announced the birth of Holly Maureen—6 lb, 8 oz.—on March 5, 1947.

1941—Dr. and Mrs. Warren W. Green announce the birth of their son Warren—born January 15, 1947.

Dr. Henry S. Swiontek has announced the opening of his office at 6623 West Cermak Rd., Berwyn, Ill.

1942—Dr. L. Tann has also resumed practice after returning from military service. His offices are at the Medical Center Building, 9 South Kedzie Avenue, Suite 200, Chicago.

1943—Dr. Nathan Horowitz has returned from military service and is resuming the practice of Medicine and Surgery at 50 W. Gunhill Road, Bronx 67, N. Y.

Dr. Sidney L. Raymon has returned from military service and is now practicing at 375 New York Avenue, Suite 203-204, Huntington, New York.

1944—Dr. David Friedman announces his return from military service and the resumption of his medical practice at 2620 Glenwood Road, Brooklyn 10, New York.

Dr. Maximilian O. Goldsmith has opened his office for the practice of Medicine and Surgery at 1221 Greenport Road, Far Rockaway, New York.

Dr. George N. Chucker resumes his practice at the Monterey Clinic, Monterey, Virginia, after his stay in the services.

1945—Several more of our alumni have recently opened offices.

Dr. Melvin Smoley, who just returned from military service, has opened his office for the general practice of Medicine and Surgery at 63.25 Saunders Street, Forest Hills, L. I., New York, N. Y.

Dr. Aaron H. Barasch has also opened his office for Medicine and Surgery at 601 W. 149th Street, New York City.

Drs. Allen Baver and Bernard Tumarkin announce the opening of offices at 1460 West Irving Park Road, Chicago 13, Ill.

Dr. Daniel Roth has opened his office at 3123 N. Clark Street, for the practice of Medicine and Surgery.

Dr. and Mrs. Daniel Halpern were awarded **Theodore Norman,** 6½ lb. son—in birth—March 24, 1947.

1946—Dr. and Mrs. Frank Guida announce the birth of their son Vincent—8 lbs, 20½ inches. He arrived February 20th of this year.

Dr. Lawrence Gluckman has opened offices at 1970 W. Lawrence Avenue, for the practice of Medicine.

1947—Dr. and Mrs. Charles M. Biren announce the birth of a son, Richard Marc—January twenty-third, nineteen hundred and forty-seven.

Dr. Walter Leonard Zielonko has announced the date of his marriage to Florence Helen Shotts of Chicago. It will be the eleventh of May.

ALUMNI RECENTY SEPARATED FROM SERVICE

1932—Nuzie, Samuel B.; Swino, John B.
1933—Sanovic, John V.
1935—Mayfield, Ike J.
1936—Sazama, John J., Jr.
1939—Constanza, Vincent A.; Taylor, Kenneth R.
1942—Farmans, Michael S.
1943—Berman, Robert A.; Schwartz, Abraham
Spinka, Harold M.
1945—Flick, Edward

QUARTERLY

At the election meeting of the Quarterly staff held on February 20, 1947, Seymour Werthamer was elected Quarterly Editor, and Samuel Liebert was elected Business Manager. Both men have had considerable experience in journalism. The former editor sends them his best wishes and largest headaches.

BOARD OF TRUSTEES

The Chicago Medical School is happy to welcome Mr. David B. Silberman to its Board of Trustees. He was born in July 1888, the son of Sigmund and Mary Silberman. He received his education at the Armour Institute and is a graduate of the University of Chicago. At present he is President of the Silberman Fur Corporation who are outstanding dealers and handlers of raw furs. His other business associations include the

Mr. David B. Silberman

Vice-Presidency of S. Silberman and Sons who specialize in the handling of raw wool. Until 1945 Mr. Silberman was on the Board of Directors of the Michael Reese Hospital for a period of nine years. The Quarterly joins the faculty and students in welcoming this outstanding Chicago businessman to the Board.

* * * * *

If you wish to save men from any particular vice, set up a tremendous cry of warning about some other, and they will all give their special efforts to the one to which attention is called.

—Charles Dudley Warner

"Derbyshire Neck" was the colloquial name for goitre in certain parts of England.

AN EVALUATION OF ECTOPIC PREGNANCY

Harold E. Silverman, M.D.
Instructor in Gynecology
The Chicago Medical School

OF ALL the conditions which befall the human female pelvis, ectopic pregnancy still seems to be the most elusive of diagnoses. There is as yet a mortality rate of 70 to 80% in cases uninterfered with, and a 3 to 5% death rate in operated cases. This is mute evidence of the fact that the diagnosis of extra-uterine pregnancy is either too often **entirely** missed, or is made only at a time when the patient has progressed to such a precarious physical state, that neither surgery nor all our other armamentaria are of avail in saving her life.

Unfortunately all cases of ectopic pregnancy do not parallel the typical textbook descriptions. More often than not, the condition makes its appearance to the accompaniment of varied non-classical symptoms and signs, which tend to lead the **unsuspecting** physician **away from** the diagnosis, rather than **to** it.

A thorough and painstaking review of the histories of 100 **proved** cases of ectopic pregnancy taken from our hospital files convinced us of the fact that most cases are **quite unorthodox,** and that only a small minority of cases are classically dramatic.

It is our belief, therefore, that a knowledge of the possible significance of certain nondescript combinations of symptoms and signs, plus a definite plan of workup of these cases should, in a great number of instances, give the physician the correct lead. This, we believe, should ultimately serve to save a life which might otherwise have been lost. It is with these views in mind that we present this brief communication.

GENERAL CONSIDERATION

The usual textbook picture of an ectopic pregnancy is that of a woman who has borne one or more children and then has remained sterile for a period of years. This period of infertility then ends in an extra-uterine pregnancy. Our series is in frank disagreement with this view, for the majority of our cases had borne children at comparatively recent dates. In only two instances was there a history of a long period of barrenness preceding the tubal accident.

The first symptoms, acording to the usual descriptions, are identical with those of normal intra-uterine pregnancy—morning sickness, fullness of the breasts, frequency of urination, and very often the history of one or more missed periods is given. So like a normal pregnancy may the early symptoms be, that not infrequently unsuccessful attempts at securing an abortion are made.

While many of the patients in our series complained of frequent urination, the majority of them exhibited some type of disturbance of menstrual rhythm. The other classical symptoms of early normal pregnancy were conspicuous only by their absence. In fact, a good many of our cases were laparotomized for some other suspected conditions, such as endometriosis, chronic pelvic inflammatory disease, ovarian cyst, etc.—and an ectopically located pregnancy was discovered at operation.

We cannot help but be impressed by these facts, and we feel that they should serve as a warning against waiting for **typical** early symptoms and signs of pregnancy before suspecting the possible existence of an ectopic gestation. For once this treacherous entity begins to develop, we have no **assurance** that it will progress to, a comparatively non-dangerous termination, such as tubal abortion, rupture into the leaves of the broad ligament, or secondary abdominal pregnancy with early death of the foetus and walling off of the process by adhesions. We must always consider the potential danger of erosion and rupture through the tubal wall with possible death of the patient before she reaches the operating table, or shortly thereafter.

NAUSEA AND VOMITING, URINARY AND BREAST SYMPTOMS

To reiterate, it was very interesting to note that our series boasted of only 12 women who complained of nausea and vomiting; only 8 had breast symptoms, but frequency of urination was a more or less conspicuous symptom.

MENSTRUAL IRREGULARITIES AND BLEEDING

Aberrations of menstruation were exhibited by 96 of the 100 studied cases. In the majority of cases, **amenorrhea** was a prominent complaint. However, there was **spotting** in place of a missed period in 14 cases, and in 11 instances there was continuous flowing in lieu of amenorrhea. In those women who were amenorrheic, spotting **followed** the missed period in most cases, while in 10 instances the amenorrhea finally led to continuous flowing. Two of our amenorrheic patients believed themselves to be "pregnant in the womb" and had criminal curettements performed. One of these suffered a tubal rupture the following day and the other within three days. One of the cases in our series whose amenorrhea was followed by continuous flowing, was curetted in the hospital after a diagnosis of incomplete uterine abortion was made. Tubal rupture followed in one week.

We believe the latter accident might be avoided if one bears in mind this fact, that in disturbed ectopic pregnancy the loss of blood from the uterus is almost never great and is usually unaccompanied by the typical labor-like cramping which attends incomplete uterine abortion. Even in cases of profuse intra-peritoneal hemorrhage, the blood lost per vagina is never proportionate to that hemorrhage. For, as John Sampson has demonstrated, while the peritoneal hemorrhage arises from ruptured or eroded tubal vessels, the blood which issues from the vagina comes from the **veins** of the uterus and never from the affected tube.

DIRECT AND REFERRED PAIN

The types of pelvic pain complained of by our patients were cutting, cramping, knife-like, boring, and dull aching. It was intermittent in the great majority of cases, being continuous only in six.

In 85% of cases, one type of bleeding or another **preceded** the pain. In only 9 instances did pain occur before the onset of bleeding. Those patients exhibited no pain whatsoever, and it is cery interesting to note that two of these had true intra-peritoneal rupture with more or less massive hemorrhage. In most cases, however, the pain was of a mild nature, and especially was this true of the cases of very recent tubal abortion and those of rupture into the leaves of the broad ligament. The most common pain complaint in those patients in whom evidence of an old disturbed ectopic was found unexpectedly during laparotomy (old blood in the leaves of the broad ligament, old clots in the free peritoneal cavity, and ancient hematosalpinx) was dull aching either intermittent or continuous.

Referred pain was a striking feature in the cases of profuse intra-peritoneal hemorrhages, and to our surprise, it was infrequently complained of in one or both shoulders. In the majority of instances, the pain was referred to the interscapular area, the costal regions, down the thighs, retrosternally, and to the base of the neck. In these cases, however, the usual signs and symptoms of massive blood loss were manifest, and the diagnosis, therefore, never in doubt. Other signs of profuse bleeding into the peritoneal cavity, such as Cullen's signs, and Salmon's signs were noted.

In the cases in which little or no intra-peritoneal hemorrhage occurred, referred pain was much less severe, and was usually complained of as shooting down the posterior aspect of one or both thighs.

FAINTING

Approximately 25% of the women in our series at some time or other complained of faintness. In those patients in whom **fainting** actually occurred, symptoms and signs of massive blood loss were more or less conspicuous. Several fainted before the occurrence of any pain whatsoever, and prior to passage of blood per vagina. Five women fainted on more than one occasion, bearing out the fact that there may be only a **single** large or small hemorrhage into the peritoneal cavity, or that there may be a succession of hemorrhages.

DIAGNOSIS

Speaking broadly, one should entertain the diagnosis of an ectopic pregnancy in any woman, who, during the period of menstrual life, complains of some type of discomfort or pain in the pelvis, if in addition there has been any change in the menstrual rhythm. In doubtful cases, proper management of the case will very often settle the issue.

MANAGEMENT

Once the bare possibility of the presence of an extra-uterine pregnancy is suspected, **the patient should immediately be hospitalized.** This holds true in the larger cities, but is of even greater importance in rural communities where doctors are often forced to travel over long distances to see their patients. If, in these small communities, a physician examines his patient and suspects an ectopic, and then allows her to remain at home, instructing her to report the sequence of events to him by telephone, she may suffer a tubal rupture before he has time to revisit her, or before she can be transported to a hospital. If, on the other hand, he had placed her in a hospital, she could have at least been carefully watched, and should a tubal accident have occurred while in the hospital, all could quickly have been put into readiness in the operating room. This difference in time might very easily be the deciding factor in the life or death of this patient.

While in the hospital the woman is put at complete bed rest, not even being allowed bathroom privileges. A thorough but careful pelvic examination is then made. The nursing staff is instructed not to administer enemas or cathartics; a liquid or soft diet and sedatives are prescribed. Then certain laboratory procedures are ordered:

1. Complete examination of a catheterized specimen of urine.
2. Test for pregnancy on a rabbit. This may or may not be positive, depending upon the **age** of the pregnancy if present, the concentration of anterior pituitary-like hormone in the urine, and the presence or absence or chorionic villi in connection with the maternal circulating blood.
3. Other more rapid tests for pregnancy, if possible, as adjuncts.
4. Complete blood count every 2 hours, for the purpose of observing:
   a. **Hemoglobin**—in which there may be a progressive drip if there is any appreciable bleeding into the peritoneal cavity.
   b. **Erythrocytes** — may parallel the decreasing hemoglobin concentration.
   c. **Leukocytes**—will usually increase as a and b decrease, due to the irritation of the peritoneal cavity by affused blood.

In cases in which there has been little or no disturbance in the ectopic gestation, the blood picture may be normal, or only very slightly altered, and a dramatic progressive drop will, of course, not be noted.

5. **Sedimentation Rate**—of the red blood corpuscles increases during pregnancy, but usually not to a noticeable extent during the early months. This holds true of ectopic gestation as well as in the intrauterine variety. However, when an ectopic has been disturbed in one way or another, and blood is effused into the peritoneal cavity in lesser or greater amount, the rate of erythrocyte sedimentation is **increased,** due to "peritoneal shock." Very often this increase is progressive, and if the sedimentation rate is repeated several times, the information, together with that obtained fro mrepeated blood counts, is invaluable.

If the above regime does not disclose information enough to satisfy the physician, the patient should be taken to the operating room and under gas inhalation anesthesia, a cul-du-sac puncture should be performed to determine the possible presence of free blood in the peritoneal cavity. If colpocentesis reveals nothing, an exploratory colpotomy should be done. The latter procedure will often settle the issue.

Should the colpotomy disclose an ectopic pregnancy, disturbed or undisturbed, the pathology may then be attacked per vagina, should the operator choose. If he prefers the abdominal route, the colpotomy wound is sutured, and the peritoneal cavity is entered by way of an abdominal incision.

The intravenous infusion of whole blood, blood plasma, and the other solutions is, of course, practiced as each individual case indicates. In the event of profuse intra-peritoneal hemorrhage, where the condition of the patient is such as to justify serious anxiety, whole blood transfusion, or infusion of plasma preparatory to operation, and during surgery becomes a life saving measure.

In conclusion, we again warn that all cases of ectopic pregnancy are not classically dramatic.

There should be no doubt as to the type of treatment once the condition is suspected; immediate hospitalization with careful observation, and the employment of proper laboratory tests should follow immediately! Once the diagnosis has been established, surgery should be done **without delay!!**

It would behoove all of us, therefore, who examine women, ever to be on the sharp lookout for the possible existence of extra-uterine pregnancy. One does not have to be a physician to diagnose the condition after tubal rupture has occurred, and when the patient is profoundly shocked. To our way of thinking, any women in the childbearing age who complains of some type of menstrual disturbance, accompanied by pelvic pain or discomfort, should be labeled as harboring an ectopic pregnancy **until proved otherwise.** Our incidence of correct diagnoses has been much higher since we have followed this axiom.

To keep in mind this treacherous entity, and to act quickly once it is suspected, may mean the saving of a life. To ignore apparently meaningless symptoms and signs, and to procrastinate may spell an invitation to disaster.

(Reprinted from Northwest Medicine)

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Book Review

DISEASES OF THE BASAL GANGALIA AND SUBTHALAMIC NUCLEI. By D. Denny Brown, M.D., C.H.B., Dr.Ph., F.R.C.P., Professor of Neurology, Harvard University, Director Neurological Unit, Boston City Hospital, Boston, Mass. Edited by Henry A. Christian, M.D., A.M., LL.D., Sc.D. (Hon.), F.A.C.P., Hon. F.R.C.P. (Canada). (Reprinted from Oxford Looseleaf Medicine with same page numbers as in that work.) Price $2.50, Oxford University Press, New York.

Described in detail are a group of diseases of the nervous system, not infrequent in occurrence, which have in common disturbance in the structure and function of the basal ganglia and subthalamic nuclei, along with associated changes in certain cortical areas of the brain.

Dr. D. Denny Brown has written, from his own large clinical experience and from his own extensive study of individual patients, this book on the diseases of the Extrapyramidal System, which will fill the needs of physicians, neurologists and neurosurgeons for information concerning the varied aspects of poor motor integration. A preliminary review of the recent literature describing the anatomy and physiology of this not too well known part of the nervous system sums up concisely that which should be known by all physicians, and following this a lengthy discussion of specific pathological entities of the Basal Ganglia and Subthalmic Nuclei are described.

* * * *

GYNECOLOGICAL AND OBSTETRICAL PATHOLOGY WITH CLINICAL AND ENDOCRINE RELATIONS. By Emil Novak, A.B., M.D., D.Sc. (Hon. Dublin) F.A.C.S. Associate in Gynecology, The Johns Hopkins Medical School; Gynecologist, Bon Secour and St. Agnes Hospitals, Balt; Fellow American Gynecological Society, American Assn. of Obstetricians, Gynecologists and Abdominal Surgeons and Southern Associations; Honorary Fellow, Societe Francais de Gynecologie; The Royal Institute of Medicine, Budapest; Sociedad d' Obstetricia et Ginecologia de Buenos Aires; Central Assn. of Obstetricians and Gynecologists; Texas State Association of Obstetricians and Gynecologists; Past Chairman, Section on Gynecology and Obstetrics, American Medical Association. Second edition, with 542 illustrations, 15 in color, 550 pages.

In some 550 pages, Dr. Novak has presented a verbal and pictoral description of pathological conditions of concern to the specialist in Obstetrics and Gynecology, and to the student and general practioner. It is of great value to anyone desiring to review the gross and histological pathologies of the female genitalia.

For the amount of material that it covers, the volume is relatively small. The material itself is presented in a very logical and orderly fashion; each section is begun with a discussion of the normal anatomy and then continues with the diseases, grouped under etiological classifications, i.e., infectious, inflammatory, neoplastic, etc. The entire work follows a definite pattern; first the diseases of the vulva, followed by the vagina, the cervix, corpus uteri, etc. The numerous illustrations and photographs accompanying the text are very lucid and lend great aid to the understanding of the textual description.

THIOURACIL* IN THE TREATMENT AND PRE-OPERATIVE PREPARATION OF THE HYPERTHYROID PATIENT

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Experimental Studies:

In 1941 the Mackenzies[1] observed that certain sulfone drugs (Fig. 1) repeatedly lowered the basal metabolic rate and produced a hyperplasia of the thyroid gland in rats. This effect was abolished by thyroid extract and thyroxin but not by Iodine. In 1942 Kennedy[2] confirmed these findings and noted that thiourea compounds were also goitrogenic and capable of producing the same effects. One year later Atwood[3] tested over one hundred various compounds of thiourea and found that of these thiouracil was the most goitrogenic. He then suggested that it be used in the treatment of hyperthyroidism. Two patients were treated by him and prompt clinical improvement resulted with a marked lowering of the basal metabolic rate. Williams[4] confirmed these findings after treating nine of his own patients the same year. Now after four years thousands of hyperthyroid patients have been treated with thiouracil at the various goitre clinics throughout the country and privately, with consistent and effective results.

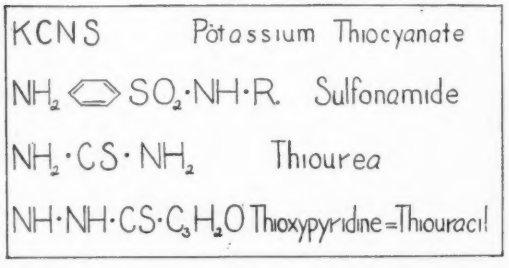

Fig.1 : Some Common Goiteroqenic Aqents Capable of Reducinq Thyroid Gland Function

Thiouracil is the one significant contribution to thyroid surgery to-day, since the reintroduction of Iodine by Plummer[5] in 1922. It is a safe and effective agent when properly administered and carefully supervised. In some cases of hyperthyroidism as in the early mildly toxic diffuse goitre patient, it obviates the need for surgery while in others it makes for a safe conduct through the operation and for a smooth post-operative recovery.

Mode of Action:

Thiouracil, like other thiourea compounds produces an enlargement of the thyroid gland. It lowers the basal metabolic rate by inhibiting the further formation of thyroid hormone—thyroxin.[6] This action takes place in the blood stream and is essentially extrathyroid, as compared to that of the action of Iodine which is intrathyroid—in the thyroid gland cell itself. In thiouracil treated rats, the thyroid gland cannot take up Iodine to form diiodotyrosine—the precursor substance of thyroxine. Some[6, 7] believe that the thiouracil unites with the Iodine and none therefore is available to form thyroxine. For this normal synthesis to take place, thyrotropic hormone made by the pituitary gland is needed and as sufficient amounts of thyroxin are made, the pituitary gland in turn is inhibited by it and thyrotropic hormone production falls. When thyroxin production is prevented by thiouracil there is no inhibition of the pituitary gland and the excessive thyrotropic hormone now formed produces an enlargement of the thyroid gland just as it does in the Iodine deficient patient with a colloid goitre of adolescence. This is a compensatory effect and result. (Fig. 2 & 3).

Clinical Findings:

Oral administration of thiouracil to the hyperthyroid patient is invariably followed by subjective improvement within four to five days. Insomnia, nervousness, tremor, palpitation and weakness are lessened. This is accompanied by steady fall in pulse rate, a rise in body weight and a fall in basal metabolic rate. Blood chemistry reveals a steady fall in the protein bound Iodine[8] and an increase in cholesterol.[9] (Fig. 4 & 5).

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*Thiouracil will soon be replaced by the less toxic and just as effective compound, propylthiouracil (propacyl).

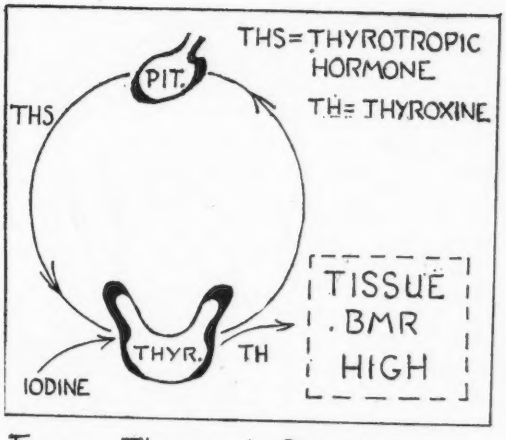

Fig 2: Thyroid-Pituitary Relationship in Hyperthyroidism

If exophthalmos is present there may be a slow regression in the amount of protrusion. In patients with advanced exophthalmos further protrusion may occur so that total destruction of vision may be threatened and even result. Williams believes this to be due to the uninhibited and overproduction of thyrotropic hormone acting on the retro-ocular tissue. Administration of small doses of thyroid extract[8, 9] may prevent this undesirable effect. The thrills and bruits felt and heard over the thyroid poles usually remain unaltered, and after several weeks of treatment the gland usually enlarges.

Effects on the Thyroid Gland:

Grossly the gland remains soft, boggy and friable. It bleeds easily because of its vascularity and lack of involution in contrast to Iodine medication.[10, 11] Histologically[12] the appearance is that of hyperplasia. The cells of the acinus remain cuboidal or columnar and the lumen of the acinus bears little colloid. The interstitial tissue is very hyperemic and infiltrated with lymphocytes. Chemical assay of the gland tissue yields a low Iodine content. From these findings it is therefore evident that thiouracil effects a chemical thyroidectomy.

Clinical Application:

Thiouracil is of value in any hyperthyroid state due to either toxic diffuse or toxic nodular goitre. It is of no value in the nontoxic types or in any other disease of the thyroid not attended by increased thyroid function.[15] The presence of cosmetic effects, mechanical disturbances to breathing, circulation and swallowing, and even exophthalmos, are not relieved by this therapy. As regards the last, it has already been stated that exophthalmos may increase. For that matter this may also occur following thyroidectomy. Explanation of this phenomenon and its correction with simple therapy is mentioned. However if this should fail and further protrusion threaten the loss of vision, a supraorbital decompression by the Nafzigger[13] method should be done without further delay.

To date I have treated the following twelve cases of various types of proved hyperthyroidism over a period of three months to three years:

6 Cases of diffuse toxic goitre—Females—Age 18-40 years. B. M. R. Plus 52 to Plus 85.

1 Case of diffuse toxic goitre—Male—Age 30. B. M. R. Plus 90.

3 Cases of toxic nodular goitre—Females—Age 55 to 58. B. M. R. Plus 38 to Plus 58. One of these was refractive and allergic to Iodine and was a cardiac and hypertensive also.

1 Case of toxic nodular goitre—Male—Age 57—B. M. R. Plus 44.

1 Case of acute thyroiditis—Female—Age 41. B. M. R. Plus 60 associated with rapid weight loss, severe sinusitis and hyperpyrexia.

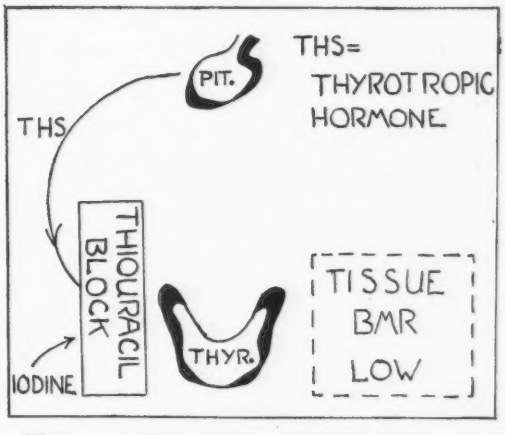

Fig.3: Thyroid-Pituitary Relationship Under Thiouracil Treatment

Only three of the twelve cases were subjected to thyroidectomy after the thyrotoxicosis was

relieved by thiouracil. These were all in the toxic nodular group. The fourth case of this group, for which surgery was not done, was in a patient who became refractive and allergic to Iodine—she also had a severe hypertension and coronary heart disease. All of the operated cases are well. Five of the diffuse toxic goitre patients are well after 18 months to three years of observation. The case of thyroiditis is well now for three years. The remaining two cases of toxic diffuse goitre have very large glands and will be later subjected to surgery after symptoms subside. Both have been under treatment for a period of only one and four months.

Dosage of Thiouracil:

In all of the twelve cases the initial dosage of the drug was 0.4 to 0.6 gm. per day in divided oral doses of 0.1 gm. each. (For each 12 Kgm. of body weight, 0.1 gm. of drug per day was given.) This dosage was used for the first month of treatment and then reduced to 0.3 to 0.4 gm. per day the second month and 0.2 to 0.3 gm. per day the third month. A maintenance dose of 0.1 to 0.2 gm. per day was used thereafter for at least one year to eighteen months. No hospitalization was necessary, except for two weeks in the case of an acute thyroiditis patient. (Fig. 4 & 5).

Precautions that Must be Taken:

To make the treatment safe and to avoid complications the following measures must be and were religiously followed:

1. Initial Blood Count:

Initial Blood Counts were made before the treatment was started, and checked once a week for the first month and then twice a month for the duration of the treatment. Any trend toward a leukopenia wherein the count falls below 4500, or toward a reduction in the granular element alone calls for immediate discontinuance of the therapy. Fortunately in none of the twelve cases did this occur.

2. At the sign of any rash, swelling, unexplained fever, arthralgia, nausea and vomiting, purpura, salivary gland swelling or other complication, prompt withdrawal of the drug is imperative. These complication will be discussed later.

3. A check on the B. M. R. was made periodically at two-week intervals. The weight curve and pulse rate were recorded every week and subjective improvement noted.

4. The dosage was always kept low. Not more than 0.6 gm. of drug per day was given to any

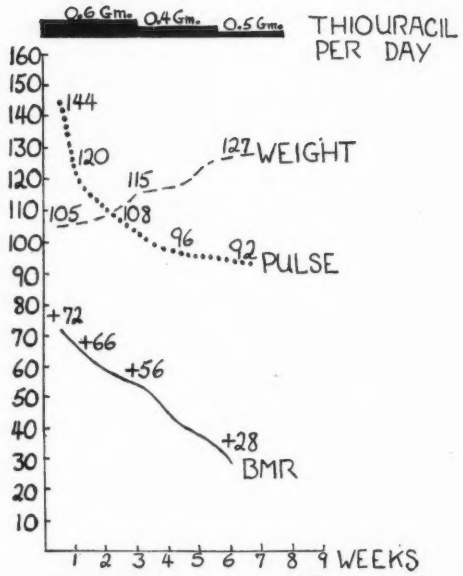

Fig 4: Response to Thiouracil in a Patient with diffuse Toxic Goiter

patient, regardless of the degree of hyperthyroidism or body weight. The amount is well below 50% of the known toxic level of the drug. Coexisting liver, cardiac, vascular, lung or kidney diseases are not effected by the drug when the dosage is kept low and therefore constitute no contraindication to its use.

5. No "crisis" cases were treated for the drug is of no value in this instance, and other measures as intravenous Iodide, oxygen, ice packs and Morphia are demanded.

. The treatment must be continued for a period of at least one year to insure against recurrence. Treatment for a period of only six to eight months has resulted in recurrence.[14]

Response to Therapy:

Prompt response to the drug was noted in all of the twelve patients except the one that had prolonged Iodine therapy and in which refractiveness and allergy developed. In this case improvement occurred after the second week of treatment. Subjective symptoms slowly disappeared and the weight curve rose, pulse rate and B. M. R. were reduced. Apparently a large back log of Iodine and Thyroxin stores had to be used up and eliminated first before a satisfactory "block" by the Thiouracil could be effected. This is approxi-

mately a one point drop in the B. M. R. for every day of Thiouracil treatment.

Thiouracil and Thyroid Surgery:

Early moderately toxic cases of the small gland type without nodulations offer the best hope for cure. Of this type of case Williams[4] believes that at least an 80% cure can be expected after one year of treatment. This period is however, too short and at least five or ten years will have to elapse before we will have the proper answer. On the other hand, toxic goitres of long standing with large diffuse or nodular glands, with or without exophthalmos, cannot be so cured.[15] It is in this group that Thiouracil becomes an important preoperative weapon.

It offers a safer conduct through the operation, and allows for a smoother and quicker postoperative convalescence. Should complications such as heart, lung, liver and kidney ailments exist, it allows ample time to correct these preoperatively without fear of refractiveness to the drug as is the case with Iodine preparations alone.

However there is one danger in surgery from Thiouracil preparation that must be ever kept in mind—*Thiouracil preparation alone will cause serious uncontrollable and even fatal bleeding at operation.*[11] To avoid this Iodine alone must be given to involute the gland for two weeks prior to operation, and for at least one week before the operation, Thiouracil must be completely withdrawn.[11]

From twenty days to six months of preoperative treatment is usually required. This depends upon the degree of hyperthyroidism. Approximately one day of treatment for each point of B. M. R. above normal, as advocated by Bartels,[10] is required. Therefore a patient having a B. M. R. of Plus 49 requires seven weeks of treatment plus a further two weeks during which time Iodine alone is given and Thiouracil completely stopped.

The Optimum Time for Surgery:

The optimum time for surgery in these cases is best stated by applying the rule of Cole[13] which demands that there be:

1. A gain in weight.
2. A reduction of pulse rate below 110 per minute.
3. A fall in B. M. R. well below Plus 45.
4. A correction of all complications.

Toxic Reactions to Thiouracil:

Eartels[17] reviewed 400 treated cases and observed 20% toxic reactions, ranging from that of a minor rash to death from agranulocytosis. These were grouped as follows:

1. Leukopenia and Agranulocytosis:

Thirty patients showed changes in the white blood count—sixteen of these showed leukopenia and nine a tendency to agranulocytosis. Of the nine, five were true agranulocytosis and three of these died. Dosage used was from 1.2 gm. down to 0.1 gm. per day and the time of onset was as early as the first week and as late as one year after treatment was instituted. This is the most dreaded complicaion and is due to destruction of the bone marrow resultant granulopenia and thrombopenia. Most reactions will occur during the first days or weeks of the treatment. When this danger threatens, the drug must be withdrawn at once and Vitamin B. Complex with pyridoxine, liver therapy, blood transfusion and huge doses of Penicillin given for it is the presence of any slight infection under these conditions that will destroy the life of the patient. As a prophylaxis it is recommended that 25 mgm. of pyridoxine be given for every 100 mgm of thiouracil used because of the good results obtained

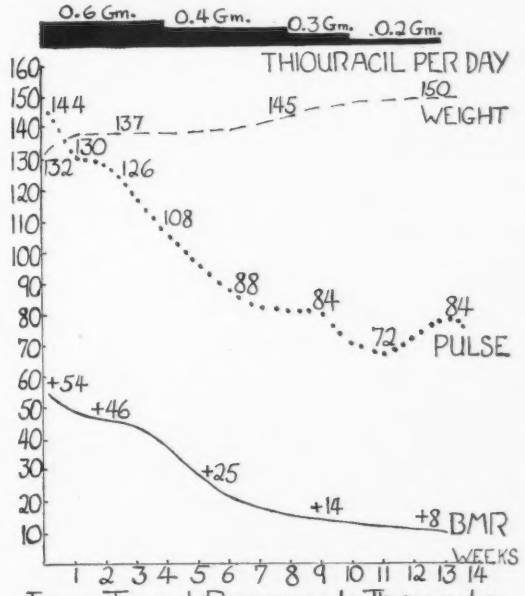

Fig. 5: Typical Response to Thiouracil in a Patient with Toxic Nodular Goiter

by the former drug in agranulocytic angina.

2. Fever, rash, pruritis and edema occurred singly or in combination in a further 36 cases.

3. Enlarged Salivary glands and Lymph nodes and arthritis occurred in another group of 6 cases.

4. Thrombocytopenia with purpura occurred in one case in which the blood count revealed a marked reduction in platelets.

5. Other minor reactions consisted of nausea, vomiting and headache in 1 case, diarrhea and jaundice in 4 cases.

All of the cases in groups 2, 3, 4 and 5 recovered quickly by prompt withdrawal of the drug. The three fatalities occurred in group 1.

REPORT OF CASES.

Eight Cases of Diffuse, Toxic Goitre:

This group comprised seven females and one male patient ranging from 18 to 40 years of age and B. M. R. of Plus 85 to Plus 40. One of the female patients had a severe thyroiditis secondary to a streptococcic sinusitis, which failed to respond to Iodine and Sulfonamide medication Prompt improvement was achieved under thiouracil and penicillin therapy. All the other cases responded promptly to thiouracil with marked improvement subjectively as was shown by a drop in pulse rate and B. M. R. and a steady gain in weight. Treatment has extended over a period of two months to three years. Two of the more recent cases, with severe degrees of hyperthyroidism, have large boggy goitres with persistent bruits and thrills over the thyroid poles and surgery is to be performed at a later date. Five of the remaining cases show no enlargement of the thyroid gland and remain free from all symptoms and signs of the disease after a treatment period of twelve to eighteen months and a further observation period of six to fourteen months. These five cases may be considered cured although a further observation will continue.

Four Cases of Toxic, Nodular Goitre:

This group comprises three female and one male patient ranging from 55 to 58 years of age and a B. M. R. of Plus 54 to Plus 38. All presented some degree of mechanical obstruction to breathing, and auricular fibrillation. One patient, a female 37 years old, with a B. M. R. of Plus 60, was allergic and refractive to iodine, had been previously psychotic and had suffered from coronary heart disease. This case was not subjected to thyroidectomy and remains controlled after a period of 32 months on an occasional maintenance dose of .1 gm. twice a week. Because of her intolerance to Iodine the gland cannot be involuted in order to render operation safe, and surgery therefore was not done.

Thyroidectomy was performed in the three other cases. All were given thiouracil over a period of 5 weeks to 2 months and a prompt return to normal pulse rate with gain in weight and reduction of B. M. R. followed. There was however, no change in the nodularity of the gland and no improvement in the subjective complaints of compression. Subtotal thyroidectomy was then done. Operative course was smooth and no untoward bleeding occurred for Iodine was given to involute the gland and Thiouracil was stopped, for two weeks prior to operation. Postoperative convalescence was smooth and uneventful. All medication was discontinued after operation and now, after from one and a half to two years, the patients remain well.

SUMMARY:

1. Thiouracil is a thyrogenic drug capable of reducing thyroid function.

2. When Thiouracil is used in proper dosage and under careful supervision it is safe and there is a prompt clinical improvement in the hyperthyroid patient.

3. The histopathology of the thyroid gland under treatment reveals a hyperplasia and vascularity with no tendency to involution as is seen under Iodine medication.

4. An explanation of Thiouracil action has been given.

5. Thiouracil is of value in any hyperthyroid state but should not be used in "thyroid crisis". It is of no value in other thyroid diseases not associated with hyperthyroidism.

6. Twelve cases of various types of hyperthyroidism were treated and the results have been given.

7. Thiouracil has the advantage over Iodine in that it can be used over a long period of time without fear of refractiveness.

8. It offers a control and in some cases even cure of hyperthyroidism, and it offers itself as a good substitute for surgery in those cases regarded as poor surgical risks due to cardiovascu-

lar renal, metabolic senile and debilitating states.

9. Preoperative method for its use has been given. To overcome the profuse bleeding at operation because of lack of involution by the drug alone, Iodine must be given and the drug withdrawn two weeks before operation.

10. Smoothness through the operative and postoperative course of the patient is noticeable feature as compared to that when Iodine preparation alone is used.

11. Toxic reactions to Thiouracil have been discussed and the need for prompt withdrawal stressed. Agranulocytosis is the most dreaded of these reactions and fatalities have occurred. Treatment has been mentioned.

12. Thiouracil aids in the treatment of Hyperthyroidism. It will cure some cases and prepare others for surgery. It will not replace thyroidectomy.

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STREPTOMYCIN. Chemicals Division of the Civilian Products Administration, Washington, D. C., Aug. 1, 1946.

Streptomycin is contraindicated in those conditions in which penicillin can be used. Recommendations for its use are listed below as well as frequent toxic symptoms. The three common methods of administration are subcutaneous, intramuscular and intrathecal, the intramuscular being preferred. The dose varies with the condition and with the mode of administration.

Indications for the use of streptomycin:

1. All case of tularemia.

2. All cases of H. influenzae infections: meningitis, endocarditis, laryngotracheitis, urinary tract infections, pulmonary infections.

3. All cases of meningitis due to: E. coli, B. proteus, B. Friedlander, B. lactis aerogenes, B. pyocyaneus, B. paratyphoid.

4. All cases of bacteria due to gram neg. org.: same as 3 except paratyphoid.

5. Urinary tract infections due to: same as 4, H. influenzae.

Helpful in the following, but its position remains undefined:

6. Peritonitis due to gram neg. bacilli.

7. B. Friedlander's pneumonia.

8. Liver abscesses due to gram neg. bacilli.

9. Cholangitis due to gram neg. bacilli.

10. Penicillin resistant, but streptomycin sensitive organisms affecting heart valves.

11. Tuberculosis.

12. Chronic pulmonary infections due to mixed gram negative flora.

13. Empyema due to gram negative infections.

Of questionable value in:

14. Typhoid fever.

15. Brucellosis.

16. Salmonella infection.

Is ineffective in:

17. All Clostridia infections.

18, Malaria.

19. Rickettsial infections.

20. Infections with moulds and fugi.

21. Virus infections.

Toxic reactions:

1. Pain and tenderness at the site of injection.
2. Headache.
3. Fever.
4. Skin Eruptions.
5. Tachycardia and fall in blood pressure.
6. Eighth nerve deafness: vertigo, tinnitus, deafness.
7. Paresthesias about the face.
8. Flushing of the skin.

* * *

SHOCK AND REFRIGERATION. Crossman & Allen. JAMA, Vol. 130, No. 4. Jan. 29, 1946., pp. 185-189.

In cases of shock, the authors advocate that large volumes of salt solution be given intravenously. This method replaces the former colloid or plasma therapy. Sodium chloride is tolerated safely in large quantities, is more conveniently and abundantly supplied, and passes most readily into the tissues to supply their specific needs for fluid and salt. Nutrient substance (glucose and amino acids) are also condemned during shock crisis because both produce rises in metabolism, entailing an increased tissue demand for oxygen. This is a danger in states of shock, however, for there is already an anoxic condition of the tissues as well as a loading of the blood with products of incomplete combustion. Such a patient requires a minimum metabolism, this principle being applied below.

The previous practice of elevating the patient's temperature through warming is no longer advocated by the authors. Instead they claim that temperature reduction should be substitued. This would result in a decrease in oxidation as well as probable toxin formation, an increased blood supply to the vital organs aided by peripheral vascular constriction and the especial relief of anoxia by the reduction of total metabolism.

* * *

MODERN TREATMENT OF CHRONIC SINUSITIS. Leland G Hannicutt, M.D., JAMA 133; 2; 84.

In order to reestablish normal sinus physiology the following two requisites must be satisfied:

1) adequate aeration of the sinus and
2) proper drainage therefrom.

This may be done medically or surgically.

It is important to bear in mind that if some local medicament is to be utilized, its pH should be such that it does not impair normal mucosal ciliary activity, or have an irritating affect on the nasal mucosa.

As a rule, in children, the treatment is one of a non-surgical nature except for removal of the infected tonsils and adenoids which are the source of the prolonged sinusitis. When pus stagnates along the nasal floor, removal by suction will permit the return of the movement of the mucous blanket and will in this way facilitate drainage from the sinus. Involved ethmoidal cells may be similarly treated; here the spot suction is applied in the upper recess of the middle meatus.

Gentle nasal irrigation with a warm solution of sodium chloride and sodium bicarbonate, after general shrinkage, aids in removing excess mucous and pus. Irrigation of the maxillary sinus vit the natural ostium is easily done in children and very beneficial.

The use of sulfa-drugs or penicillin locally or parenterally is of questionable value here as well as for any chronic infection.

It has been found that with most of the chronically infected sinuses, it is the rare case where the sinus mucosa cannot be restored to useful function if present knowledge of medical treatment is carried out.

Surgically speaking, an obstructing septum will require a submucous resection while a polyp will require removal. It times the middle turbinate may create an inadequate space in the middle meatus and refraction is therefore indicated. With a large turbinal cell in the middle turbinate, crushing of the cell is the treatment of choice.

When conservative therapy fails in chronic maxillary sinusitis a window may be surgically created in the region of the inferior meatus. If suppuration still continues (usually due to a polypoid lining), the mucosal lining may have to be removed.

With a stubborn ethmoidal infection, ethmoidectomy may have to be resorted to, while a chronic sphenoid sinusitis may necessitate an enlargement of its natural ostium. If conservative treatment of frontal sinus infection fails, the Lynch operation in some form is utilized.

* * *

"Simplicity of manner is the last attainment. Men are very long afraid of being natural, from the dread of being taken for ordinary."

—Jeffrey

PLANTAR NEUROMAS, MORTON TOE. Surg. Gyn. & Obst. -84; 1; 47. William H. Bickel, M.D., Malcolm B. Dockerty, M. D.

Morton first described this clinical entity as a painful affliction of the fourth metatarsophalangeal articulation. He treated the condition by excising the metatarsophalangeal joint and the surrounding soft tissue, including "the nerves distributed around the joint". Diseased tissues were not identified by him.

Later, Hoadley noted the presence of a smali neuroma on one of the digital branches of the lateral plantar nerve to the fourth toe; resection of the nerve offered a prompt and perfect cure.

Clinically these patients have severe paroxysms of pain, which usually arise beneath the heads of the third and fourth metatarsals and extend into the opposing sides of the third and fourth digits. This pain may extend up the posterior aspect of the leg as far as the hip and the attack is brought on most commonly while the victim is walking. Physically one will note a well localized tender spot on producing pressure over the neuroma site.

Treatment may first be conservative such as wearing shoes of sufficient length and width, suitable padding within. If symptoms persist, surgery must be undertaken. The proximal end of the nerve is severel well back into the short muscles of the foot and thus future irritation of the inevitably amputated neuroma is avoided.

Stress was made on early ambulation and weight bearing when a dorsal or web splitting incision is made.

"Let us return now to Narvaez and a black man whom he brought covered with smallpox, and a very black affair it was for New Spain, for it was owing to him that the whole country was stricken and filled with it, from which there was great mortality, for according to what the Indians said they had never had such a disease, and, as they did not understand it, they bathed very often, and on that account a great number of them died; . . ."

—True History of the Conquest of New Spain by Bernal Diaz, a soldier under . . . Cortes

The rooster's legs are straight.

The boy's are not.

The rooster got plenty of vitamin D.

Fortunately, extreme cases of rickets such as the one above illustrated are comparatively rare nowadays, due to the widespread prophylactic use of vitamin D recommended by the medical profession.

One of the surest and easiest means of routinely administering vitamin D (and vitamin A) to children is MEAD'S OLEUM PERCOMORPHUM WITH OTHER FISH-LIVER OILS AND VIOSTEROL. Supplied in 10-cc. and 50-cc. bottles. Also supplied in bottles of 50 and 250 capsules. Council Accepted. All Mead Products Are Council Accepted.

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Wherever he is

YOUR RED CROSS IS AT HIS SIDE